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13. ABSTRACT

The ultimate fate of the coronary vein grafts is not known. They already are a major palliative tool with many hundred of grateful beneficiaries. Whether or not they will be long-lasting palliation and thus applicable to a wide group of patients with coronary arterial disease is yet to be determined. Since coronary disease forms a major portion of any internist's problems, it is obviously of great importance to keep up with the latest information in this rapidly changing field. This is the purpose of this issue of Present Concepts and the hope of its authors.

The symposium consists of six articles, each a review of a vital problem in the treatment of patients with coronary artery disease from the patients with severe incapacitating angina and proximal lesions now being advised to have coronary bypass surgery to the patient with an arrhythmia who is being treated with digitalis for whom a dosage determination is vital. The titles of the six articles are: "Measurement of ventricular function in arteriosclerotic heart disease", "Cardiac time intervals. Use in the bedside evaluation of cardiac performance in man", "Myocardial revascularization", "Surgically treatable complications of acute myocardial infarction", "Echocardiography", and "Serum digitalis levels. New techniques of measure".

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PRESENT CONCEPTS IN INTERNAL MEDICINE

GUEST EDITOR FOR APRIL 1971

COL Melvin D. Cheitlin, MC

Chief, Cardiology Service

ASSISTANT EDITOR

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LETTERMAN GENERAL HOSPITAL

Presidio of San Francisco, California 94129

Colonel Melvin D. Cheitlin, MC, has been Chief of the Cardiovascular Service at Letterman General Hospital from 25 June 1968 to July 1971. His leadership, professionalism and dedication has been unsurpassed. His stature as a cardiologist has been recognized not only by our staff but also by the civilian medical community in the San Francisco Bay Area. Nor have his talents gone unrecognized by The Surgeon General — as evidenced by his new assignment as Chief of the Cardiovascular Disease Service, Walter Reed General Hospital and consultant in cardiology to The Surgeon General, United States Army.

A combination of competent specialist, outstanding teacher and enlightened researcher are qualities not often found in one individual —
Colonel Cheitlin embraces this triad.

To you, Mel, a cherished friend and a respected colleague, we dedicate this issue of PRESENT CONCEPTS and wish you continued success and happiness in your new assignment — we will miss you.

THE MEDICAL STAFF
LETTERMAN GENERAL HOSPITAL

PRESENT CONCEPTS IN INTERNAL MEDICINE

VOLUME IV *April 1971* Number 4

CARDIOLOGY

SYMPOSIUM

CONTENTS

Foreword 291

ARTICLES

MEASUREMENT OF VENTRICULAR FUNCTION IN ARTERIOSCLEROTIC HEART DISEASE 293
COL Melvin D. Cheitlin, MC

CARDIAC TIME INTERVALS. Use in the Bedside Evaluation of Cardiac Performance in Man 311
MAJ David R. McConahay, MC

MYOCARDIAL REVASCULARIZATION 335
LTC John P. Nagle, MC

SURGICALLY TREATABLE COMPLICATIONS OF ACUTE MYOCARDIAL INFARCTION 353
MAJ Bruce H. Brundage, MC

ECHOCARDIOGRAPHY 361
MAJ Richard S. White, MC

SERUM DIGITALIS LEVELS. New Techniques of Measurement 375
MAJ Carroll M. Martin, Jr., MC

Department of Medicine

LETTERMAN GENERAL HOSPITAL

FORTHCOMING SYMPOSIA. . .

ALLERGY *(originally announced as the April issue)*

RHEUMATOLOGY

PULMONARY DISEASES

and others

FOREWORD

Over the past 20 years advances in diagnostic and medical and surgical therapeutic maneuvers have changed the practice of cardiology radically. Congenital, hypertensive, and valvular heart disease have been benefited the most by these new approaches. A recent major advance in the treatment of coronary artery disease, our largest problem, has been the development of the Intensive Care Concept including minute-to-minute monitoring of the electrocardiogram. There has been a reduction of mortality in acute myocardial infarction from 30-35 percent to 15-20 percent. There have been many attempts to improve the blood supply to the myocardium beyond the areas of obstruction, some with only spotty success and all with only questionable objective improvement. Over the last three years we have seen the development of surgical techniques, such as saphenous vein bypass grafts and gas endarterectomy, that convincingly accomplish this goal of revascularization. Still there are major unsolved problems before we can unhesitatingly recommend these procedures to all those who are anatomically amenable to them. First, and perhaps foremost, is the lack of knowledge about the fate of these grafts: how long will they stay patent? Secondly, once we know this, we must also know the natural history of the patient with coronary disease. We have a great mass of natural history information, most of it dating from precoronary arteriography days, about the fate of the patient who has had a myocardial infarction or who just begins to have angina pectoris. What we don't know, as yet, is what happens to the coronary artery that is diseased. Does the plaque progressively narrow, does it stay stable for long periods of time, does it suddenly occlude, and if so, what are the changes of this catastrophic happening? Until these questions are answered our recommendations to patients *vis-à-vis* coronary artery surgery simply reflect the enthusiasm or lack of it which we have for the procedure

The state of the art is such that patients with severe incapacitating angina and proximal lesions are now being advised to have coronary bypass surgery. Whether or not revascularization improves ventricular function is still not known. Certainly it is possible that chronically ischemic muscle may be responsible, at least in part, for the decreased function. If this is the case, then reversal of

the ischemia can reasonably be expected to improve function. It is known that the poorer the ventricular function, the higher the mortality of the surgery. In this issue of *Present Concepts*, I have attempted to review briefly the problem of evaluation of ventricular function in coronary artery disease.

Doctor McConahay has taken the task of reviewing the indirect techniques being developed which show great promise in detecting changes in ventricular function. These techniques are noninvasive and can be repeatedly done on an outpatient status.

Doctor Nagle reviews the present status of surgery in coronary arterial disease and puts into perspective the promises and dangers of the various procedures.

Doctor Brundage reviews those areas of cardiovascular surgery aside from revascularization which can benefit certain hemodynamic problems in patients with arteriosclerotic heart disease.

Doctor White, taking up the description of indirect, noninvasive techniques, reviews the use in cardiology of reflected ultrasound utilized in echocardiography. This technique in its ability to detect changes in chamber size, holds great promise in noninvasively looking at measures of ventricular function such as ejection fraction, end-diastolic volume, and rate of ejection.

Doctor Martin, in departure from our major theme, reviews the new techniques of measurement of serum digitalis levels. These newly developed tests have great importance in that they promise a solution to the not uncommon therapeutic dilemma of too much versus too little digitalis in a patient with an arrhythmia.

The ultimate fate of the coronary vein grafts is not known. They already are a major palliative tool with many hundred of grateful beneficiaries. Whether or not they will be long-lasting palliation and thus applicable to a wide group of patients with coronary arterial disease is yet to be determined. Since coronary disease forms a major portion of any internist's problems, it is obviously of great importance to keep up with the latest information in this rapidly changing field. This is the purpose of this issue of *Present Concepts* and the hope of its authors.

— COL MELVIN D. CHEITLIN, MC
Guest Editor

MEASUREMENT OF VENTRICULAR FUNCTION IN ARTERIOSCLEROTIC HEART DISEASE

COL Melvin D. Cheitlin, MC

Recently, with the development of surgical techniques which appear promising in their ability to revascularize the myocardium, it has become most important to quantitate the degree of ventricular muscle impairment as accurately as possible so as to determine whether revascularization or removal of nonfunctional areas of the myocardium could be expected to improve the patient's clinical situation. The purpose of this paper is to discuss the function of the ventricle in chronic coronary arterial disease and our present means of evaluating this function in the laboratory.

There are a number of reasons for myocardial dysfunction in arteriosclerotic heart disease including muscle scar, transiently ischemic muscle, asynergy, and mitral insufficiency.

Muscle Scar

This takes the form of either localized conglomerate scar, the residual of an old myocardial infarction, or diffuse fibrous tissue, perhaps the residual of years of intermittent ischemia. This fibrous tissue results from the loss of contractile muscle mass causing a decrease in the ability of the ventricle to develop tension. There may also be a change in the compliance characteristics or "distensibility" of the ventricle. The ventricle becomes stiffer and requires a higher ventricular filling pressure to achieve a given change in ventricular volume, thus interfering with the heart's function as a pump.

Transiently Ischemic Muscle

Reversible ischemia causes a decrease in contractility or loss of function in this segment of muscle. These ischemic areas are only transiently impaired and when the demand for excess myocardial oxygen decreases (i.e. exercise stops), the localized area of ischemia is reversed and function returns. Depending on the amount of ventricular muscle involved, the

ventricular function may or may not be transiently detectably altered. Evidence of this reversible change in myocardial function is seen in those instances in the catheterization laboratory when angina occurs accompanied by a rise in pulmonary wedge pressure or left ventricular end-diastolic pressure (LVEDP). The clinical counterpart of this is seen in the patient who develops with angina a transient atrial or ventricular gallop which disappears as the angina subsides.

Asynergy

In addition to individual segments failing to function as muscle strips, there is the decreased ability of the entire ventricle to function in a coordinated manner, i.e. to function as a pump. The heart may be thought of as a group of muscle spirals surrounding a lumen. This hollow muscle ejects blood by a properly coordinated, sequential contraction organized in this way by depolarization over a specific conduction network. This ejection results from a slapping motion of the ventricle giving momentum to the blood and propelling it out of the ventricle. This action requires the maximum development of tension in the muscle wall early in systole. The ventricular lumen then reduces in size to the extent of the stroke volume. To provide this impetus, the proper coordination of contraction is essential. Harrison and his group /1,2/ and later Herman et al /3/ demonstrated this lack of coordination in contraction in many patients with coronary disease, the so-called "asynergy" of the ventricular contraction. This asynergy is expressed as either the entire ventricular muscle contracting hypodynamically, or as portions of the muscle contracting poorly compared to other parts, or even expanding as other parts of the ventricle contract. The ultimate in this "uncooperativeness" is present when each muscle fascicle contracts without relation to any of the others, a condition recognized as ventricular fibrillation.

With lesser degrees of loss of coordinated contraction, there is a dissipation of contractile energy used in just changing the shape of the ventricle The most striking example of this is seen in the ventricular aneurysm. This contractile energy is lost to the useful work of the heart; namely, expelling the stroke volume. In addition, these areas are not themselves contributing contractile energy to the systole, and so the remaining muscle fibers have to work harder to achieve any given level of intraventricular pressure.

Mitral Insufficiency

The mitral valve mechanism depends for its proper function on the integrity of the papillary muscles, chordae tendinae, and especially on the functional integrity of the attachment of papillary muscles to the ventricular wall. Any mitral insufficiency allows a low resistance runoff from the ventricle, thus competing with the aorta for the ventricular ejectate.

REVIEW OF FUNCTION OF THE HEART AS A MUSCLE AND AS A PUMP

The job of the heart is to supply blood to the body in amounts sufficient to meet the body's demand under all physiologic circumstances. If the heart does this without encroaching on its reserves — in other words, with normal filling pressures and ventricular volumes, we consider the heart to be functioning normally.

The principle ways in which the heart accomplishes the task of changing its output to meet the body's demands are by changes in heart rate and stroke volume.

cardiac output (cc/min) = stroke volume (cc/beat) x heart rate (beats/min)

Stroke volume is dependent on several variables — "preload", "afterload", rate of contractility, and the synergy of the contraction./4/

"Preload" or diastolic ventricular filling. Here is one of the fundamental properties of muscle described in the Frank Starling principle which states that with all other factors held constant, the greater the resting length of the muscle at the onset of contraction, the greater the force generated by that contraction./5/ This property of cardiac function has been called "heterometric autoregulation" and implies that the normal heart can eject whatever volume comes back to it. This increase in the force of contraction does not involve an increase in contractility or the maximum rate at which the ventricle contracts. In the intact heart, this

"resting fiber length" or "preload" is represented by the end-diastolic volume. This in turn is related to the end-diastolic pressure by the curve of ventricular compliance or distensibility. Figure 1.

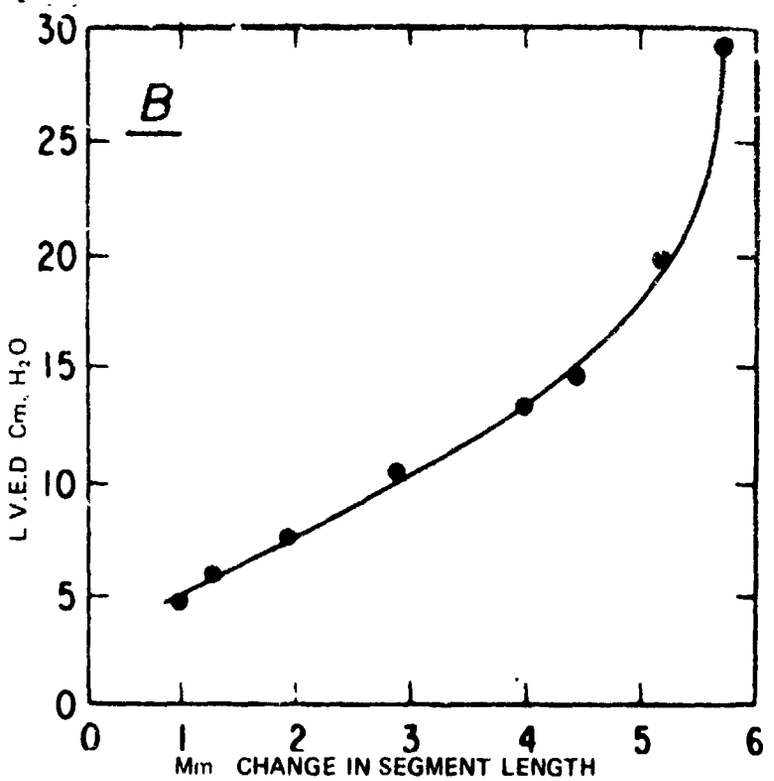

Fig 1 Ventricular compliance relating to left ventricular end-diastolic pressure with ventricular volume. *Amer J Med* May 1961, page 749. *Reproduced with permission.*

Normally the ventricle operates at the diastolic volume where the compliance curve is flat and great increases in ventricular volume can occur with only small increases in ventricular diastolic pressure. As diastolic volume increases, the compliance curve becomes steeper. If the muscle thickness increases, as occurs in hypertrophy, or changes as in fibrosis, the ventricle becomes less compliant and for further increases in ventricular filling there is much greater increase in diastolic filling pressure.

The usual way those stretch-force relationships are presented graphically is in the form of a "ventricular function curve" where the stroke volume (or its derivative, cardiac work) is plotted against end-diastolic volume or end-diastolic pressure. Figure 2.

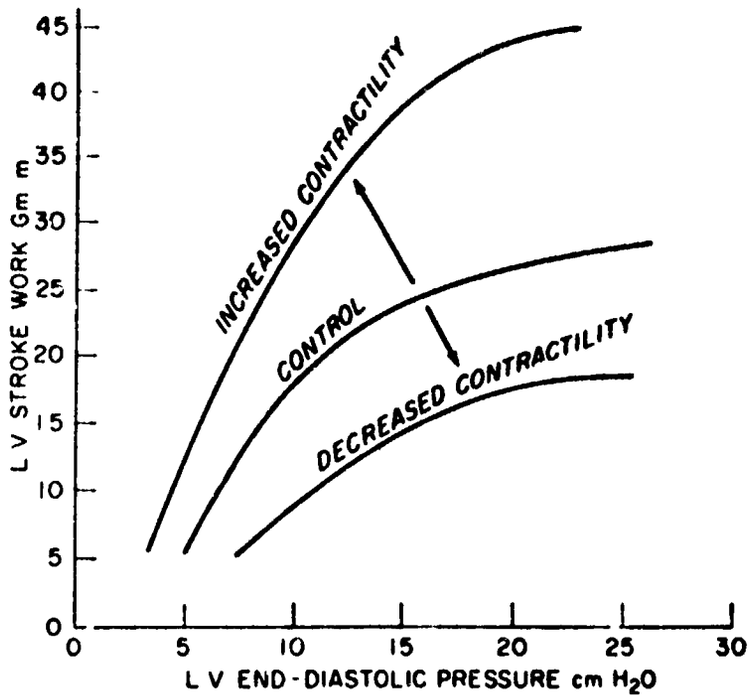

Fig.2. Hypothetical function curves of the left ventricle indicating the shifts in the curve that occur with alterations in myocardial contractile state. This diagram provides a useful framework for considering the directional responses of the human ventricle to various forms of stress. *(See text, Ann Intern Med* 70:369 (Feb) 1969, Ross J Jr, discussant, Fig 6, page 375.) *Reproduced with permission.*

"Afterload" is a term applied to myocardial wall stress during systole. This can be thought of as the work the heart does on ejecting its stroke volume and relates principally to the development of myocardial wall tension during systolic contraction. Wall tension is related to intraventricular pressure, the radius and the thickness of the ventricle by the LaPlace relationship:/6/

$$T \propto \frac{IP \cdot R}{2h}$$

T = tension
IP = intraventricular pressure
R = radius h = thickness of ventricle

Afterload is determined chiefly by the size of the heart as well as by peripheral factors, those variables that influence aortic pressure such as systemic arteriolar resistance and arterial elasticity. This ability of the heart to eject the same stroke volume against a wide range of resistances has been termed "homeometric autoregulation":/5/

Contractility or Inotropic State. Increases in contractility or the maximum rate at which the myocardium develops tension can be brought about physiologically by increases in sympathetic stimulation, by increasing heart rate, by endogenous catecholamines, (epinephrine and norepinephrine), and iatrogenically by drugs such as digitalis and isoproterenol. Isolated muscle studies have shown that the maximal velocity of muscle shortening at zero load (V_{max}) is characteristic of the contractile state of the muscle and independent of the initial muscle length./7/ Figure 3.

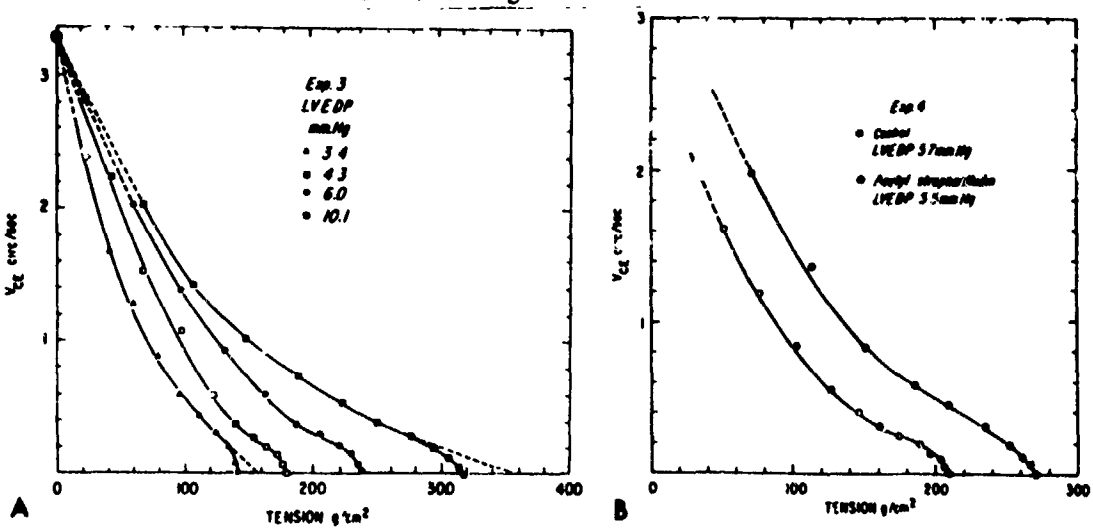

Fig. 3. Relation between V ce (contractile element velocity) and ventricular wall tension (or stress) in dog ventricle. Each curve obtained from single isovolumic contractions. A. Effects of increasing preload (LVEDP) on force velocity relation. Tension augmented without change in V max, velocity of shortening at zero load. B. Effects of acetylstrophanthidin on force–velocity relations of normal dog ventricle. Both V max and isovolumic tension augmented. *(Reproduced with permission from* Sonnenblick EH et al *Prog Cardiov Dis* 12 449-466 (Mar) 1970.)

Synergy of Contraction. This has already been discussed. If each muscle fiber is working at maximum capacity but there is lack of coordination, obviously the heart will not function as a pump.

In the normal resting individual there is little sympathetic autonomic influence. With muscular exercise the demand for increase in cardiac output is met primarily by increased sympathetic activity increasing heart rate and contractility as well as decreased peripheral arteriolar resistance in the exercising muscles. The normal individual does not call on cardiac reserve present in the Frank Starling mechanism to meet this demand for cardiac output. Therefore, the diastolic volume may remain the same or even decrease with exercise, but it does not increase. If there is difficulty with ventricular function such as a primary decrease in contractility or loss

of ventricular functional units, then this increase in sympathetic tone is not enough and the Frank Starling mechanism is brought into play. There is then an increased diastolic filling of the ventricle, an increased force of ejection, and the stroke volume is normalized by this mechanism. The price of keeping the stroke volume normal has been that the diastolic volume is increased, thus causing an increased left ventricular filling pressure (LVEDP). There is a limit to the utilization of this mechanism in that complicance of the ventricle is such that LVEDP rises, causing an increase in pressure behind the ventricle in the systemic and pulmonary venous circuit. This finally results in the classic signs and symptoms of pulmonary and systemic venous congestion (gallop rhythm, dyspnea, orthopnea, hepatomegaly, and edema). Eventually the heart cannot keep up the cardiac output and fatigue is the primary symptom, at first with exercise and finally at rest.

LABORATORY EVALUATION OF VENTRICULAR FUNCTION

We are cognizant that no matter what measurement we use there remain patients with coronary disease who respond normally. The spectrum of ventricular dysfunction ranges from the most subtle abnormalities to the most flagrant. An ideal evaluation would look at all the factors mentioned separately and evaluate each one's effect on the ventricular function.

Experimental and clinical methods of evaluating myocardial function in the intact human being include (a) resting values — cardiac output, stroke volume and LVEDP; (b) ventricular function curves — relating stroke volume or cardiac work to LVEDP before and after stress; (c) "afterload" stress; (d) "exercise factor"; (e) contractility, velocity of contraction (NOTE: the indirect methods of measurement are not discussed because of other papers in this symposium); (e) ejection fraction.

Resting Values

The classic method for evaluating ventricular function relies on measuring LVEDP or its correlates: left atrial mean pressure, pulmonary artery wedge pressure, pulmonary artery end-diastolic pressure, or pulmonary artery mean pressure. This is then correlated with cardiac output or stroke volume in the basal state. It is well-recognized that many patients with severely compromised ventricles can have these vasal measurements perfectly

normal, and in general this is the case in many patients with coronary arterial disease. Generally, the greater the compromise of the coronary arterial system, the more likely one is to have these relatively insensitive parameters abnormal. Because these resting values are frequently normal, the patient has been stressed by a variety of means to bring out abnormalities.

Ventircular Function Curves

In this evaluation the cardiac output, stroke, volume, or one of its derivatives such as cardiac work, is measured before and after stress. The type of challenge most often given is muscular exercise /8/ but a variety of other stresses have been used such as atrial pacing /9,10/ or isoproterenol./11/ In normal individuals the LVEDP usually falls by one or two millimeters of mercury, but if on exercise or atrial pacing there is a decreased ventricular function, there is no fall or even a rise in LVEDP. Thus, the Frank Starling mechanism forms the basis for the classic ventricular function curve, where stroke volume or its derivatives is plotted against left ventricular and diastolic volume or pressure. Figure 4.

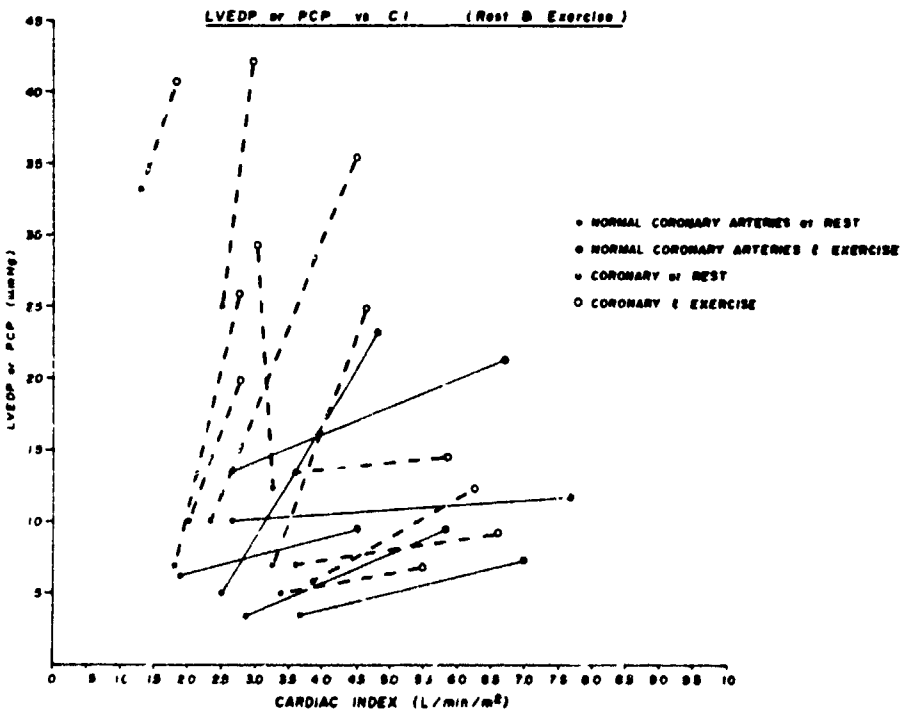

Fig 4. Ventricular function curves from Letterman General Hospital experience, 1970.

"Exercise Factor"

It is desirable to correlate the ability to increase cardiac output with the degree of increased demand for cardiac output as manifested by increased total oxygen consumption. This has been approached by measuring cardiac output at rest and after exercise and dividing this by the increase in oxygen consumption produced by that exercise. This ratio of increased cardiac output in cc/min to each 100 cc/min increase in oxygen consumption has been called the "exercise factor"./13/ In normal persons the cardiac output rises by more than 600 cc/min for each 100 cc/min increase in oxygen consumption. Unfortunately, there is a great overlap at degrees of exercise causing small increases in oxygen consumption between normal people and people with myocardial disease. If the patient can be stressed maximally, where the oxygen saturation in the pulmonary artery falls to 30 percent or lower, there can be a better separation of patients from normals because a normal person can achieve a cardiac output of 7.0 L/min/m^2 body surface area whereas any degree of ventricular impairment does not allow this to be achieved. Figure 6. In coronary artery disease, angina is usually the limiting factor and such heavy exercise cannot be tolerated.

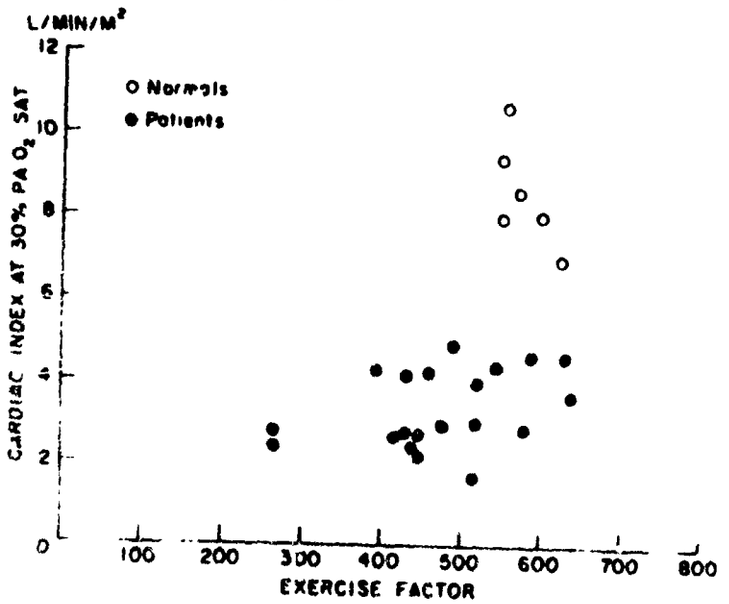

Fig 6 Relation between cardiac index at a pulmonary arterial O_2 saturation of 30 percent and the exercise factor in normal subjects (open circles) and patients with cardiac disease (closed circles). *From* Epstein SE et al. Exercise in patients with heart disease. Effects of body position and type and intensity of exercise. *Amer J Cardiol* 23:572, 1969. *Reproduced with permission of The American Heart Association, Inc.* From Epstein et al. *Circulation* 35 1049, 1967

"Afterload" Stress

The myocardium can be stressed by changing the aortic pressure by arteriolar vasoconstriction using methoxamine or angiotensin./12/ Points can be obtained in the ventricular function curve relating changes in LVEDP to cardiac output. Normally, the left ventricle can eject a similar stroke volume against a wide range of afterloads ("homeometric autoregulation). When ventricular function is decreased, there is a decreased ability to eject this stroke volume and so a fall in cardiac output occurs. Figure 5.

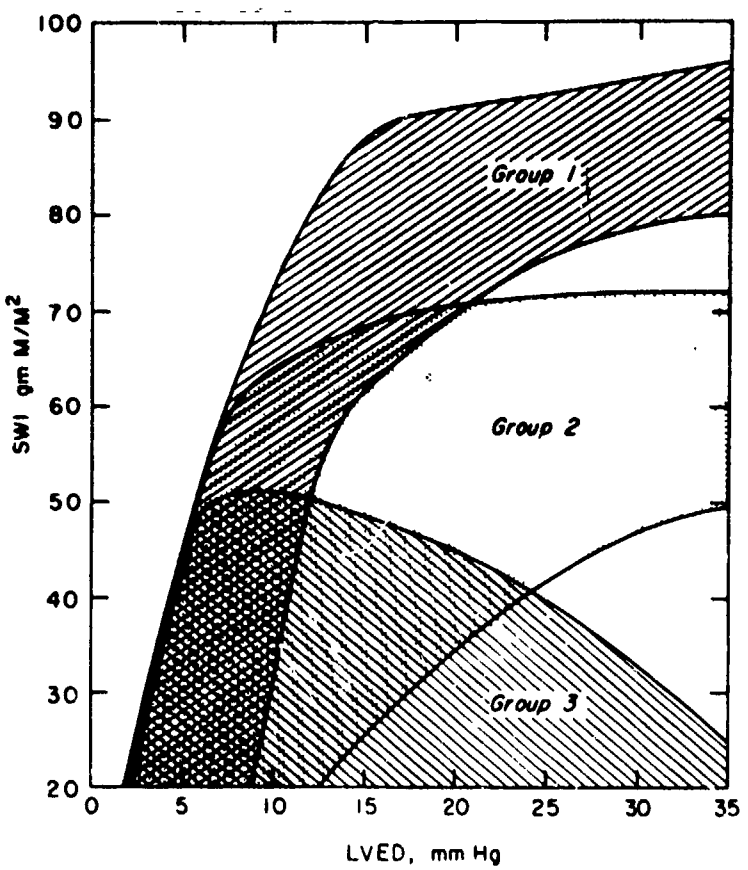

Fig 5 Diagram showing comparison of "afterload" stress after angiotensin infusion. Groups 1 to 3 represent patients with increasing abnormal ventricular function. *From* Ross J Jr, Braunwald E: The study of left ventricular function in man by increasing resistance to ventricular ejection with angiotensin. *Circulation* 29 739, 1964. *Reproduced by permission of The American Heart Association, Inc.*

Contractility

The first derivative of the left ventricular pressure curve (dP/dt), or the peak velocity of intraventricular pressure development has been shown to be a sensitive indicator of the level of ventricular contractility./14/ Most of the time pressure curves are obtained with manometers at the end of a fluid-filled catheter system. Although technically dP/dt derived from this type of curve is acceptable if critical damping of the system is achieved, to avoid artefacts an end-catheter micromanometer has been designed and with this a faithful recording of the dP/dt can be obtained. Peak dP/dt occurs at the time of aortic valve opening, i.e. at the peak of isovolumic contraction./14/ Figure 7.

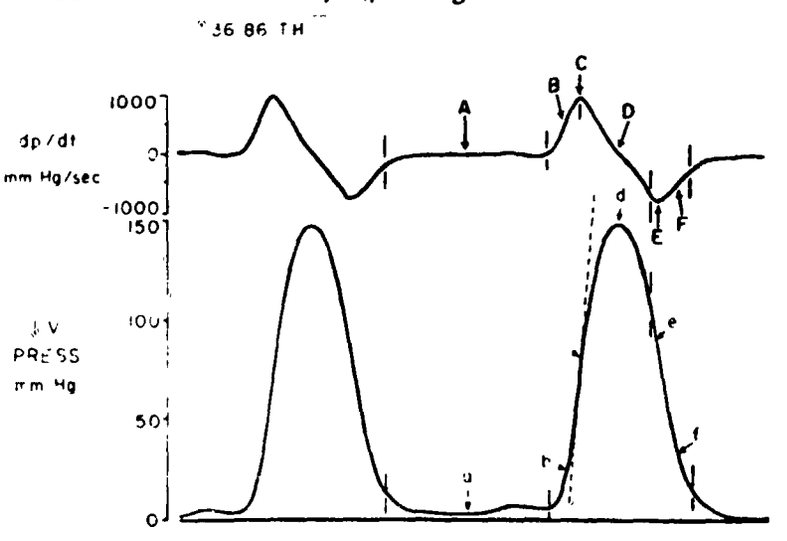

Fig. 7. Simultaneous recordings of left ventricular pressure pulse (LV) and first derivative of left ventricular pressure (dP/dt) in patient with aortic valve prosthesis. The various portions of the first derivative and the corresponding segments of the pressure recording from which they were computed are labeled. During ventricular filling when rate of change of ventricular pressure is minimal, dP/dt is flat at a level near zero (segment A). With the onset of isovolumic contraction, dP/dt rises slowly and then rapidly (segment B) to reach the peak dP/dt (point C), the maximal rate of pressure rise, indicated by slope of the diagonal broken line. Peak dP/dt usually occurs at instant of opening of semilunar valves, thus at peak isovolumic ventricular pressure. If aortic diastolic pressure is raised to a very high level, peak dP/dt may occur prior to opening of the aortic valve. During early and middle phases of ventricular ejection, dP/dt descends to the baseline, and during late ejection, as intraventricular pressure decreases, dP/dt becomes negative (segment D). The rate of decrease of ventricular pressure is maximal at point F during isovolumic relaxation (segment F). Left ventricular pressure was recorded by direct needle puncture *(Reproduced by permission of the author and source, Amer J Cardiol* 23:516, 1969.)

This has been used as a measure of contractility. Unfortunately peak dP/dt is a complex factor depending on loading conditions of the myocardium as well as contractile state. For instance,

an increase in LVEDP or increase in aortic diastolic pressure increases dP/dt. It thus appears that dP/dt is relatively well-preserved during early decreases in ventricular function, mainly by the Frank Starling mechanism.

Attempts to overcome these problems have been made by measuring the dP/dt in different patients at the same common peak isovolumic pressures, thus minimizing the afterload effect, and dividing this dP/dt by a measurement of end-diastolic volume, thus minimizing preload effects./15/

Actual quantitation of the velocity of contraction of the contractile element would be a much more accurate measure of contractility if it could be independent of loading effects on the ventricle. However, measurement of ventricular volume, muscle wall thickness, as well as instantaneous intraventricular pressure is necessary. These, so far, have been obtainable only with angiocardiographic techniques and many sequential measurements are needed to calculate wall stress and velocity of contraction./16/ Noninvasive techniques such as echocardiography and radioangiography are becoming available for the beat-to-beat measurement of wall thickness and ventricular volume, but these methods are still in the process of being developed./17,18/ The calculation of velocity of ventricular contraction and change of wall tension is still laborious and is therefore only used in research studies.

A more recent approach has taken advantage of the fact that during isovolumic contraction there is little change in the geometry of the ventricle (thickness of the left ventricular muscle and radius of the left ventricle). Since maximal dP/dt and wall tension is reached at the end of isovolumic contraction it has been possible to use the intraventricular pressure curve and simultaneous dP/dt in place of the wall tension and its first derivative to estimate the actual velocity of the contractile element (Vce) during isovolumic contraction./11/

By plotting the calculated Vce against the simultaneous intraventricular pressure, it is possible to get enough points during isovolumic contraction to extrapolate back to zero tension development and get a measurement of maximum velocity of contraction (Vmax). This has been an exciting and valuable development in the approach to the evaluation of myocardial contractility in valvular disease because it separates loading effects from contractility as such. Unfortunately, since there is such heterogeneity of contractility, such diffuse

and local collections of scar tissue, and such frequent dyner gic contraction in coronary artery disease, one must realize that in order to derive Vmax from the pressure curve alone, it is likely that all the assumptions which one must make are not even close to reality. Figure 8.

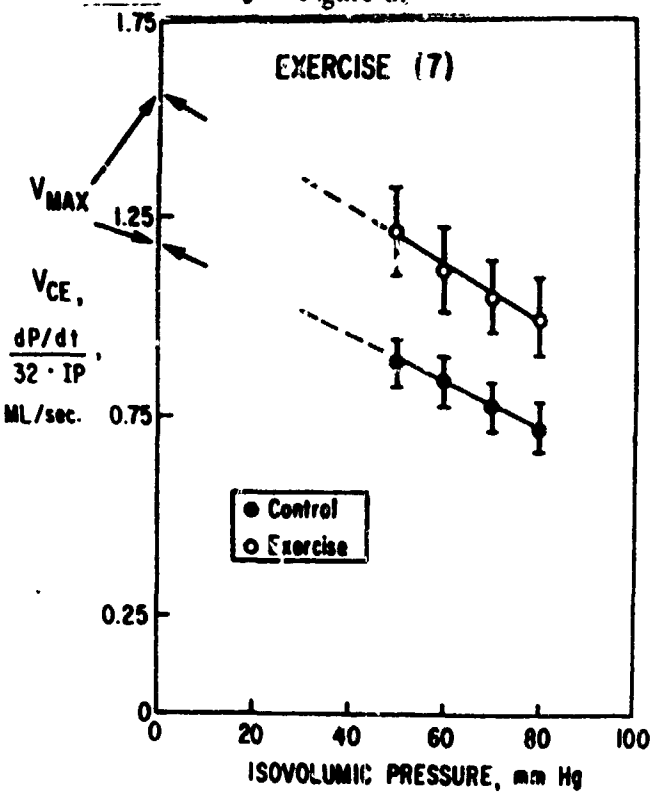

Fig. 8. Pressure-velocity relation during isovolumic contraction before and during leg exercise in a patient with an aortic valve prosthesis. Contractile element velocity (V_{CE}) was determined as V_{CE} = dP/dt divided by the product of its corresponding isovolumic pressure and the series elastic constant. The curves were constructed by relating V_{CE} to isovolumic pressure at 5 msec. intervals from the onset of contraction to the opening of the aortic valve. Extrapolation of the isvolumic segment of both curves to the maximal velocity of isotonic shortening(V_{max})is indicated by the broken lines. *(Reproduced by permission.)* /11/

It is apparent that although this will be a field further investigated, at present it is not clinically useful in coronary disease.

Recently, under the impetus of work by Weissler and others /19/ there has been a reawakened interest in the indirect measurements of the time of isovolumic contraction which is directly related to dP/dt. With a decrease in myocardial function, the rate of development of ventricular pressure is less (dP/dt is decreased)/ By simultaneous measurement of ECG, indirect carotid pulse, and phonocardiogram, it is possible to measure with good reproducibility the time intervals of several

pertinent systolic events which reflect the duration of isovolumic contraction (preejection period (PEP) and left ventricular ejection time (LVET)). With decreasing left ventricular function, there is an increase in PEP and a decrease in LVET. Since these two measurements diverge as ventricular function decreases, the ratio of PEP/LVET is even more sensitive in separating normals from patients with decreased left ventricular function. If these measurements prove to be stable enough in any individual over a period of time and to change enough with ventricular dysfunction to be detectable before obvious clinical deterioration, this simply done outpatient measurement may prove to be valuable in following the ventricular function in patients with arteriosclerotic heart disease. This topic is discussed in detail in pages *311-334* of this symposium.

Ejection Fraction

Since the ultimate question is whether the ventricular stroke volume is adequate or not for the physiologic situation, evaluation of the left ventricular contraction by cineangiography has proved to be most helpful. By this method we can calculate the degree of asynchrony present in the contraction as well as the percent of end-diastolic volume (EDV) ejected with each stroke, i.e. the ejection fraction.

Normally over a wide range of diastolic filling volumes and afterloads, the ratio of stroke volume (SV) to end-diastolic volume (EDV) or percent of EDV ejected is kept constant at 60 to 80 percent. /20/ If there is a decrease in contractility, the ejection fraction will decrease below normal. /21/ Left ventricular angiograms done in the right anterior oblique (RAO) position enable us to measure the end-systolic and end-diastolic volumes, and by subtraction, the stroke volume. Therefore, from these angiograms, the SV/EDV, or ejection fraction, can be measured. Figures 9 and 10.

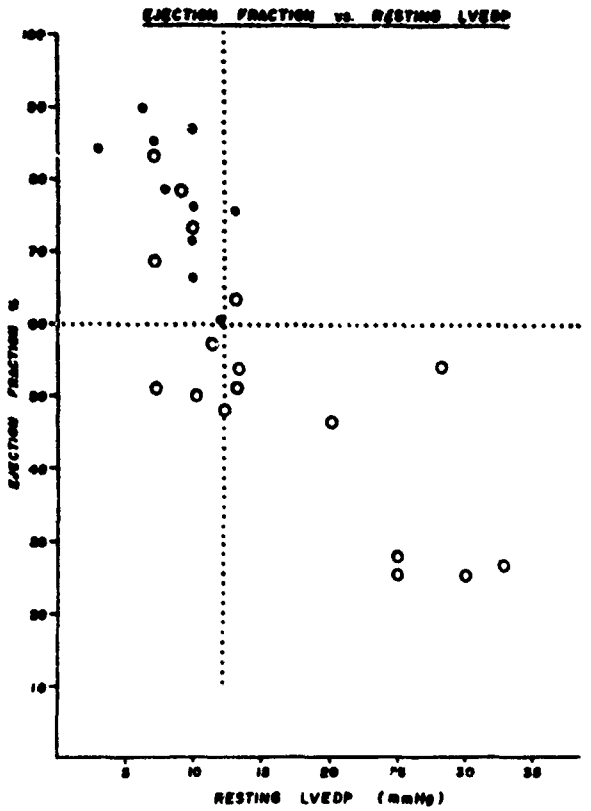

Fig 9. Letterman General Hospital Experience, 1970, correlating fraction with left ventricular end-diastolic pressure. Dotted lines indicate limits of normality.

● Normal coronary artery

○ Coronary disease

Fig. 10. Cineangiogram in right anterior oblique view with superimposed drawings of ventricular contraction. End-diastole = 1; end-systole = 5. There is hypokinesis of diaphragmatic surface caused by diaphragmatic infarction.

COMMENT

We recognize that no one measurement will pick up an abnormality in every patient with coronary disease. In fact there is good evidence /23/ that abnormalities of ventricular function are more common the greater the number of obstructed coronary arteries a patient has. When evaluating patients with coronary disease for surgery, however, we consider that those patients who can (1) perform submaximal work without an increase in LVEDP, (2) can increase cardiac output appropriate to the increase in total body oxygen consumption, and (3) can eject a normal percent of their EDV (normal ejection fraction) are for all practical purposes still functioning "normally". It is certainly possible that they may have a decrease in their maximal ability to function, but this decrease probably has little clinical significance when evaluated in terms of whether or not they will benefit from a surgical procedure. We also have found that the greater the number of functional abnormalities the more probable it is that the person has a seriously compromised ventricle. If we can show that the compromise is on the basis of dyssynergic contraction or diastolic overload (by mitral insufficiency or aortic insufficiency) and that the ejection fraction is still normal in spite of the large left ventricular end-diastolic volume or high LVEDP, then we can hope to improve the patient's condition by surgically relieving him of this excess hemodynamic burden.

It has been suggested that there is improvement in ventricular function after bypass of coronary arterial obstruction by saphenous vein grafts. So far, this is still a suggestion and we must await serial studies of ventricular function in order to prove such a speculation. What is certain at the present time is that the more compromised the ventricular function, the higher is the mortality rate and the lesser the benefit derived from coronary revascularization. For these reasons it is imperative to define the status of ventricular function to the best of our ability in those patients being considered for surgical coronary revascularization.

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CARDIAC TIME INTERVALS
Use in the Bedside Evaluation of Cardiac Performance in Man

MAJ David R. McDonahay, MC

For many years, cardiovascular physiologists have endeavored to translate information obtained from graphic records of the acoustic and pulsatile phenomena of the cardiac apex, precordium, and arteries, into meaningful clinical measurements of the heart's performance in man. Much useful data have been gleaned from an analysis of the contour of these pulsations but until recently few clinically applicable expressions of cardiac performance had evolved. With the awareness that the temporal phenomena of the cardiac contraction cycle may provide a bedside measure of cardiac function, there has been a resurgence of enthusiasm for the noninvasive evaluation of cardiovascular dynamics and myocardial performance. It is now appreciated that changes in the more usual expressions of cardiac function such as volumes, flows, or pressures, are accompanied by alterations in the temporal course of the cardiac cycle which can be recorded and measured by presently available graphic techniques. Measurement of such systolic and diastolic time intervals using a simultaneously recorded indirect carotid pulse tracing, electrocardiogram, phonocardiogram, and apexcardiogram may offer a safe, convenient, reproducible, and potentially continuous means of detecting changes in such dynamic variables in left ventricular (LV) function as cardiac output, stroke volume, myocardial "contractility", left ventricular dp/dt, and left ventricular ejection fraction./1/ The use of these time intervals as prognostic indicators in patients with acute myocardial infarction is presently being explored; and the application of these intervals in the indirect assessment of left ventricular myocardial function in patients with chronic coronary heart disease is also being investigated./2,3/ Use of these techniques also allows a noninvasive serial assessment of cardiac performance in patients with valvular heart disease before and following prosthetic valve insertion with the potential capacity for detecting subtle alterations suggesting prosthetic dysfunction. Such techniques may even find use in the fields of aerospace and oceanography when more practical and effective methods are required for monitoring circulatory changes and the effects of gravitational stress on the human circulation.

Optimal appreciation of these auscultatory and palpatory findings requires certain "present concepts" of the electrical and mechanical events occurring during the normal cardiac cycle. Before discussing each of the time intervals of the cycle, a brief review of the indirect reference tracings used in the derivation of these intervals will be presented with emphasis on the genesis of each tracing's component parts and on the rationale for selecting certain of these parts for the measurement of the various cardiac intervals.

INDIRECT REFERENCE TRACINGS

ELECTROCARDIOGRAM (ECG)

The standard limb lead which inscribes the earliest deflection, preferably a well-defined Q wave, is selected for measurement of the onset of ventricular depolarization. Lead II most commonly fulfills these criteria.

INDIRECT CAROTID PULSE TRACING

A record of the carotid arterial pulse is obtained from the right carotid artery at the point of maximal pulsation between the sternoclavicular joint and the angle of the jaw with the subject's face turned slightly to the left. The carotid pulse wave represents the transmission of the central pressure wave generated by the rapid displacement of blood from the left ventricle into the aorta. Two points must be clearly defined for the purposes of measuring systolic time intervals: (1) the point of origin of the upstroke of the carotid artery percussion wave (CA_u), the peak of which represents peak aortic flow, and (2) the steep downward deflection interrupting the descending limb of the pressure pulse, the trough of which represents the incisura (CA_{In}) separating the systolic and diastolic phases of the carotid pulse. This CA_{In} is related to the closure of the aortic valve.

The CA_u defines the moment of onset of the left ventricular ejection if correction is made for the time required for transmission of the pulse wave from the ascending aorta to the carotid artery (pulse transmission time = PTT). This PTT may be defined as the interval between the aortic component of the second heart sound (A2) on the phonocardiogram and CA_{In} because

A2 coincides with the CA_{In} in the absence of a delay in pulse transmission. The indirect carotid tracing is also a superior reference tracing for the timing and identification of A2 and thus for the separation of A2 from the pulmonic component of the second heart sound.

PHONOCARDIOGRAM [4,5]

Phonocardiography is basically the graphic representation of the sounds originating in the heart and great vessels. The recent use of precise instrumentation with simultaneous recordings of intracardiac sound and pressure events in conjunction with cineangiographic procedures has shown that an abrupt change in local blood flow, i.e. sudden acceleration or deceleration within the "cardiohemic" system, is responsible for the production of heart sounds./6,7/ Any sudden obstruction to blood flow as a result of sudden tensing of an intracardiac structure as it reaches its elastic limits results in a corresponding sudden change in the blood's momentum. Consequently, the entire system is set into vibration — the high frequency vibrations are appreciated as heart sounds and the lower frequency components as pressure phenomena.

First Heart Sound (M1) [7-10]

In the normal cardiac cycle, as the left ventricular pressure rises initially during isovolumic contraction, mechanical forces are generated which induce a ballooning of the apposed mitral valve leaflets toward the left atrium as the mitral valve apparatus ascends away from the apex./11/ As these leaflets, and their papillary muscles and chordae tendinae, are stretched to their elastic limits and this mitral ascent is abruptly stopped, blood flow in that direction is suddenly decelerated; vibrations of all left ventricular structures including the closed mitral valve are then established coincident with both the inscription of the peak of the left atrial "c" wave and the mitral component of the first heart sound (M1). It is important to appreciate that the pressure crossover between the left atrial and left ventricular pressures with the associated mitral valve closure occurs during the ascent phase of the mitral apparatus and therefore actually anticipates the first heart sound by 15-30 milliseconds. M1 itself is generated not by the collision of the mitral valve margins but by the deceleration of blood which occurs as the mitral valve reaches the point of its maximal ascent./12/

Second Heart Sound (A2)

During the remainder of systole the mitral valve complex is again drawn toward the left ventricular apex. The aortic component of the second heart sound (A2) then occurs near the peak of the left atrial "v" wave as the left ventricular pressure is falling. Classically, A2 has been assumed to be due to closure of the aortic valve but has recently been shown to begin at the onset of the phase of rapid deceleration of forward aortic flow coincident with the trough of the incisura of the central aortic pulse. The onset of this rapid deceleration phase actually occurs while forward flow is still going on and, in fact, occurs approximately 25 milliseconds before the nadir of aortic flow, the latter being the point at which the aortic valve presumably closes./9/

Third Heart Sound (S3) and Fourth Heart Sound (S4)

The other commonly described heart sounds are likewise currently attributed to abrupt acceleration or deceleration of local blood flow. The third heart sound (S3) whether a physiologic left ventricular filling sound or the protodiastolic gallop of congestive heart failure is related to transient vibrations or oscillations resulting from deceleration of the rapid inflow of blood into the left ventricle as the limits of ventricular relaxation are reached. This S3 closely coincides with the peak of the rapid filling wave (RFW) of the apexcardiogram as described below. Similarly, a fourth heart sound (S4) may be attributed to oscillations set into motion by decelerating blood as it strikes a noncompliant left ventricle following left atrial contraction.

Opening Snap (O.S) /7,10/

The opening snap (O.S.) in mitral valvular stenosis occurs after the peak of the left atrial "v" wave and after the crossover of the left atrial and left ventricular pressure curves./11/ This O.S. coincides with the end of the downward movement of the mitral apparatus when the mitral valve is abruptly halted at the point of its maximal downward excursion. Again, the entire cardiac system of valves, blood, and walls is presumably thrown into a state of vibration from this sudden deceleration, and the resulting high frequency vibrations are recorded as sound phenomena on the phonocardiogram. This O.S. approximates

the "O" point on the apexcardiogram and can thereby be easily differentiated from an S3 which occurs somewhat later on the apexcardiogram near or at the peak of the rapid filling wave.

APEXCARDIOGRAM [13-19]

The apexcardiogram (ACG) is an indirect means of evaluating left ventricular function by recording low frequency, i.e. 0.1 - 20.0 cycles per second (c.p.s.), displacements of the chest wall over the cardiac apex. Tracings obtained in this manner can be used to time certain cardiac events such as atrial systole, the onset of left ventricular contraction, and mitral valve opening and to evaluate not only the onset but also the rate of left ventricular filling. The ACG is the only indirect method available for assessing the diastolic events of the left ventricle. To record an ACG, the point of maximal impulse at the apex is identified by palpation and the left ventricular origin of this impulse confirmed by recording an ECG from this point. A microphone transducer is then applied by hand to the chest wall at this point, and the ACG is recorded in mid-expiration. The outward and inward movements of the apical impulse in normal individuals are graphically shown on the bottom (ACG) curve in Figure 1.*

"A" wave. A small "A" wave representing left atrial contraction is coincident with the fourth heart sound (S4) on the phonocardiogram and occurs shortly after the P wave of the ECG.

ACG_u and "E" point. A brisk upstroke (ACG_u), beginning 20 - 30 milliseconds after the onset of the QRS complex and coinciding with the onset of left ventricular contraction, represents the rapid systolic wave which reaches a maximal peak (Ejection or "E" point) at a time approximating mitral valve closure and aortic valve opening.

"O" point. After the "E" point, a rapid fall off and then a plateau, and finally another sharp and rapid drop at the end of systole is recorded which reaches a nadir ("O" point) near the time of AV valve opening and the beginning of the rapid diastolic filling phase of the left ventricle.

RFW. Subsequent early diastolic filling is represented by a sharp rise to a definite peak (rapid filling wave - RFW), this peak being coincident with an S3 as recorded on the phonocardiogram.

*Figure 1 appears on the next page. Since reference is made repeatedly to this figure a copy on a blue card has also been placed in an envelope attached to the inside of the back cover of the symposium. We hope that it will be helpful to the reader to have this figure "mobile". — EDITOR

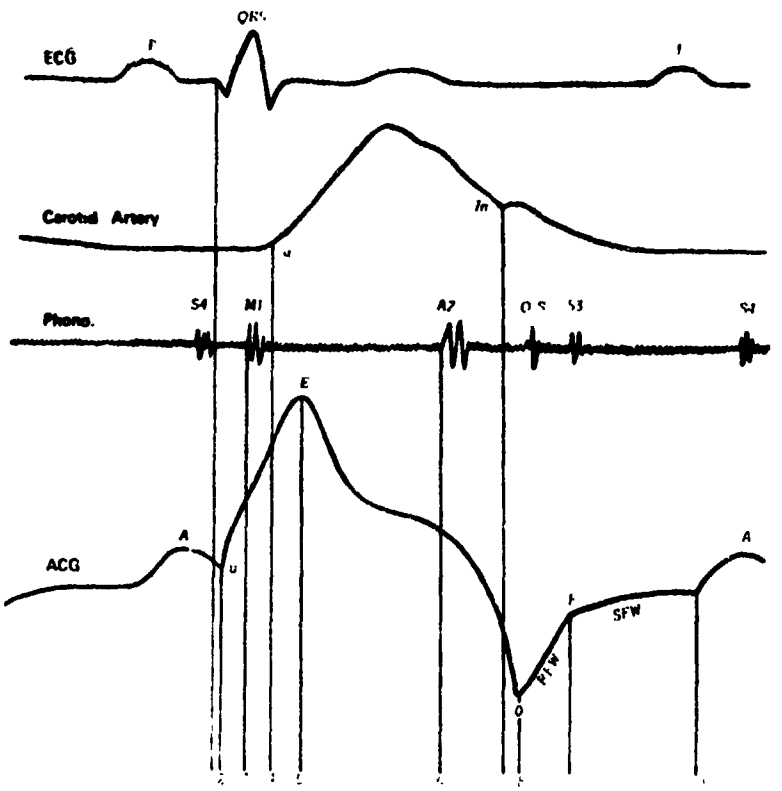

FIG 1 **Indirect Reference Tracings.**
The points indicated in the diagram are used in measurement of cardiac time intervals. The vertical lines *(numbered left to right 1 through 10)* have been drawn so as to denote sequence of events and to aid in the comparative reading of the four types of indirect reference tracings.

ECG = electrocardiogram with *P-wave* and *QRS-wave complex* indicated

Carotid Artery = indirect carotid artery pulse tracing
u = upstroke [point of origin of the carotid artery upstroke (CA_u)]
In = carotid incisura [point separating systolic and diastolic phases of carotid pulse (CA_{In})]

Phono. = phonocardiogram
S4 = fourth heart sound
M1 = initial high frequency vibrations of mitral component of first heart sound
A2 = initial high frequency vibrations of aortic component of second heart sound
O.S. = opening snap
S3 = third heart sound

ACG = apexcardiogram
A = left atrial contraction
u = upstroke of ACG
E = ejection point
O = nadir
RFW = rapid filling wave
SFW = slow filling wave

SFW. From this point, the RFW is replaced by a slower rising wave (slow filling wave - SFW) which ends at the level of the succeeding "A" wave at the completion of passive diastolic filling.

Comment

Several points regarding these components of the ACG deserve further comment. The "A" wave represents the effect of the left atrial contraction on left ventricular filling (the "atrial kick") and thus provides a measure of the compliance characteristics or distensibility of the left ventricle. With a reduction in myocardial compliance, commonly seen in the presence of left ventricular hypertrophy or myocardial ischemia, a more forceful left atrial contraction is required to complete ventricular filling, and necessarily a more prominent "A" wave is generated./20/ When the amplitude of this "A" wave exceeds 15 percent of the total deflection of the ACG, an impedence to left ventricular filling should be suspected./21-23/ In the presence of atrial fibrillation or mitral stenosis, this "A" wave is absent.

The onset of the initial rapid systolic wave (ACG_u) occurs approximately 25 milliseconds after the QECG and represents the first detectible mechanical event of left ventricular systole, i.e. an increase in left ventricular intramural pressure which anticipates the initial rise of left ventricular intracavitary pressure by 15-20 milliseconds.

The ACG also enables one to differentiate the splitting of the first heart sound (S1) from a systolic ejection click because the former precedes the systolic peak ("E" point") by approximately 20 milliseconds whereas the latter follows this "E" point by 40-80 milliseconds. The ACG is also extremely useful in identifying a mitral opening snap (O.S.) and distinguishing it from either the second heart sound or an S3. Although the "O" point is actually delayed 15-30 milliseconds after the crossing of the left atrial and left ventricular pressure curves in patients with mitral stenosis, the approximation of this "O" point and an early diastolic sound provides the best confirmatory evidence that this sound is in fact an O.S. As already stated, an S3 would coincide closely with the peak of the subsequent rapid filling wave.

Thus, the ACG is a complex tracing which reflects not only intracardiac pressure events, but also changes in left atrial function and left ventricular volume, compliance, and position.

CARDIAC TIME INTERVALS*

With this knowledge of the underlying intracardiac electrical and mechanical events as they relate to portions of each reference tracing, we can now better appreciate the hemodynamic significance of the time intervals derived from these indirect tracings and explain most of the alterations in these intervals which occur with certain mechanical, pharmacologic, or pathologic interventions. The cardiac cycle may be divided into the following phases:/24/

PHASE	EXPLANATION
Total electromechanical systole	*page 318*
Pre-ejection period	*page 319*
Electromechanical lag	*page 320*
Isovolumic contraction time	*page 321*
Left ventricular ejection time	*page 324*
Protodiastole	*page 325*
Isometric relaxation time	*page 326*
Rapid inflow period	*page 327*
Slow inflow period (diastasis)	*page 327*
Atrial systole	*page 327*

Total electromechanical systole *(1-6)*

Total electromechanical systole encompasses the entire period of left ventricular systole from the onset of the ventricular depolarization as measured by the onset of the QRS complex on the ECG (Q) to the first high frequency vibrations of the aortic component of the second heart sound (A2). This Q-A2 interval may be influenced by many interventions (Table I), but is best considered in terms of its component parts, the pre-ejection period and left ventricular ejection period.

**APPENDIX, page 334* provides the reader with a referenced list of "normal" values.

TABLE I

TOTAL ELECTROMECHANICAL SYSTOLE

Shortened by...	*Prolonged by...*	*Unaffected by...*
Tachycardia	Left bundle branch block	Congestive heart failure
Acute myocardial infarct	Aortic stenosis and insufficiency	Change in stroke volume
Inotropic interventions (digitalis, epinephrine)	Increasing age	Change in aortic pressure
Amyl nitrite		Change in aortic pressure
↑ serum [Ca++]		Respiration
		Right bundle branch block

Pre-ejection period *(1-6 minus 4-7, Figure 1)*[125]

The pre-ejection period (PEP), the period from the onset of electrical systole to the onset of actual left ventricular ejection, is obtained by subtracting the left ventricular ejection time (LVET) from the total electromechanical systole (Q-A2). This interval is responsive to a number of interventions (Table II), but the pathophysiologic significance of these changes in PEP are ideally appreciated in terms of the changes in the two intervals making up the PEP, i.e. the electromechanical lag and the isovolumic contraction time.

TABLE II

PRE-EJECTION PERIOD

Shortened by...	*Prolonged by...*	*Unaffected by...*
Exercise-induced tachycardia	Aortic hypertension	Atropine or pacing-induced tachycardia
↑ stroke volume	Congestive heart failure	Respiration
↑ cardiac output	Left bundle branch block	Right bundle branch block
Inotropic intervention (digitalis, isoproterenol)	Acute myocardial infarct	
Amyl nitrite	↓ stroke volume	
Hyperthyroidism	↓ cardiac output	
Aortic hypotension	↑ left ventricular end-diastolic pressure	
Aortic stenosis and insufficiency	↑ extent of coronary artery disease	
	Passive head up tilting	
	Hypothyroidism	
	Pulsus alternans	
	Increasing age	

Electromechanical lag [26] *(1-2 or 1-3, Figure 1)*

The electromechanical lag represents the delay in onset of left ventricular mechanical activity following the spread of electrical activity across the ventricle. The onset of this interval is defined by the onset of the ventricular depolarization as recorded on the ECG (Q). However, the onset of the mechanical events is still disputed and has been most commonly defined as either the initial high frequency vibrations of the first heart sound (M1) as recorded on the phonocardiogram, or the beginning of the rapid upstroke of the apexcardiogram (ACG_u). Since this ACG upstroke represents the change in configuration of the left ventricle with the earliest detectable movement of left ventricular contraction coincident with the rise in intramural pressure, and since it actually precedes by 15 milliseconds the left ventricular intracavitary pressure rise, the ACG offers the best source for detecting the onset of left ventricular mechanical activity./24/ In the absence of a suitable ACG, the use of M1 will suffice although it occurs approximately 20 milliseconds after the onset of left ventricular mechanical activity.

Significance of electromechanical lag

The electromechanical lag represents the time necessary for the conduction of an electrical impulse throughout the myocardium and for the translation of this electrical energy into mechanical activity. At the myocardial cellular level, this lag results from complex ionic changes across the cell membrane and from the subsequent activation of the contractile elements of the myocardial fibers (excitation-contraction coupling). The Q-M1 interval which is commonly measured has the same physiologic significance as the time required for the ascent phase of the mitral valve complex which is related to the motion of the mitral annulus. The Q-M1 may be prolonged by many factors (TABLE III), one of the most important clinically being mitral stenosis./27/ This prolongation in mitral stenosis is attributed to the longer time required by the left ventricle to develop pressure sufficient to drive the mitral valve to a point of maximal upward excursion in the presence of an increased left atrial end-diastolic pressure. If the Q-M1 exceeds 80 msec, severe mitral stenosis is often present.

Unfortunately, the electromechanical lag is often too brief to permit accurate reproducible measurements.

TABLE III

ELECTROMECHANICAL LAG

Prolonged in...
Systemic hypertension
Congestive heart failure
Left bundle branch block
Acute myocardial infarct
Mitral stenosis
Wolff-Parkinson-White syndrome
Ventricular septal defect
Atrial septal defect
Patent ductus arteriosus
Ebstein's anomaly
Aortic insufficiency

Isovolumic contraction time [28,29] *(2·4 minus 6·7, 2·5, 3·5, 3·4 minus 6·7, or 3·6 minus 4·7, Figure 1)*

The isovolumic contraction time (IVCT) begins with the onset of LV myocardial tension and ends with the onset of LV ejection. Initially the LV wall tension is translated into movement detectible by the ACG, and then into rising intracavitary pressure without a corresponding change in volume. The IVCT ends when the LV intracavitary pressure exceeds the aortic diastolic pressure at which time the aortic valve opens and a rapid reduction in LV volume occurs coincident with ejection. Many different methods have been used in an attempt to define the IVCT indirectly; the most reliable of these uses the rapid upstroke of the ACG (ACG_u) to define the onset of left ventricular muscle tension and the upstroke of the indirect carotid pulse (CA_u) corrected for the delay in pulse transmission as the point coincident with the onset of LV ejection. The correction factor for pulse transmission time (PTT) in the equation $IVCT = ACG_u - (CA_u - PTT)$ represents the lag in central pulse transmission from aortic root to carotid artery and is defined as the interval between A2 on the phonocardiogram and the trough of the incisura of the carotid pulse tracing since A2 should virtually coincide with this incisura in the absence of a pulse transmission delay.

The use of M1 to indicate the beginning of left ventricular wall tension is less optimal because it occurs after the onset

of mechanical activity, and because its timing may occasionally be varied by simply changing the position of the microphone transducer. Likewise, using the ejection crest or "E point" of the apexcardiogram to define the onset of left ventricular ejection is unsatisfactory because this point actually follows LV ejection and the initial aortic pressure rise by 35-40 milliseconds.

In patients with an aortic valvular prosthesis, the IVCT may be estimated by measuring the interval from M1 to the prosthetic opening click.

Significance of IVCT

The factors reported to affect the pre-ejection period (PEP) have been shown to exert closely similar changes in the duration of the IVCT (TABLE IV). In fact, since the electromechanical lag is so brief, changes in the PEP result mainly from changes in its major component, the IVCT. Thus, the implications of alterations in either of these intervals are essentially the same, so they will be discussed together.

TABLE IV

ISOVOLUMIC CONTRACTION TIME

Shortened by...	*Prolonged by...*	*Unaffected by...*
↑ stroke volume	Aortic hypertension	Age
Inotropic interventions (digitalis, sympathetic stimulation, catecholamines)	Congestive heart failure	Pacing-induced tachycardia
	Left bundle branch block	
	Acute myocardial infarct	
Tachycardia	↓ stroke volume	
Hyperthyroidism	↓ left ventricular dp/dt or "contractility"	
	Hypothyroidism	
	Bradycardia	
	Pulsus alternans	

The PEP and IVCT offer a nontraumatic means of estimating the velocity of isometric contraction of the myocardium and therefore indirectly a means of estimating myocardial "contractility". This "contractility" (as mirrored by the IVCT) is a major determinant of myocardial O_2 consumption, and in fact, most of the O_2 consumed by the myocardium is used to create tension during this period of isovolumic contraction. The PEP and IVCT represent a direct expression of a sum of the factors comprising "contractility",

especially the left ventricular dp/dt, or the rapidity with which the left ventricle generates pressure during isovolumic contraction to the point of ejection./30/ This LV dp/dt, the key determinant of the IVCT, is a linear function of the product of left ventricular end-diastolic stretch and volume; and the ratio of LV dp/dt to the integrated isovolumic tension is currently widely used as a more quantitative measure of myocardial "contractility". The duration of the IVCT and PEP varies inversely with LV dp/dt, which is, in turn, directly related to "contractility"./31/ Thus, the IVCT and PEP provide an index, if only an approximation, of these crucial interrelated parameters of left ventricular function.

Any factor which compromises myocardial "contractility" or the ability of the myocardium to generate pressure rapidly will prolong the IVCT and PEP. Therefore, a deficient rate of myocardial force development secondary to defects in either the number, organization, or synchrony of the myofibers as found in congestive heart failure will increase the time required for the intraventricular pressure to attain aortic diastolic levels. This lengthening of the IVCT in the face of a relatively constant total duration of electromechanical systole will necessarily encroach on or shorten the subsequent systolic ejection period and reduce stroke volume. Also, a reduced velocity of myocardial fiber shortening during this abbreviated period of left ventricular ejection will further diminish the expected stroke volume.

This dependency of the IVCT and PEP on myocardial "contractility" and on the rate of rise of LV pressure during isovolumic contraction (LV dp/dt) explains the alterations in these systolic time intervals in patients with coronary heart disease. PEP prolongation has been found to be directly proportional to the number of coronary arteries involved at coronary arteriography. /32/ Measurements of the IVCT also may permit statistical separation of patients with chronic coronary heart disease from those with acute myocardial infarction /33/ and have been found to be most prolonged in patients with extensive fatal infarcts. In fact, one study found significant progressive alterations in PEP and left ventricular ejection time in patients with increasingly severe manifestations of coronary heart disease, i.e. noninfarcts but known coronary heart disease < acute subendocardial infarcts < acute nonfatal transmural infarcts < acute fatal transmural infarcts./34/

The intervals, PEP and IVCT, are also dependent on the left ventricular and aortic pressures and the differences between these

pressures from the onset of LV contraction to the onset of ejection. At a constant left ventricular end-diastolic pressure and constant LV dp/dt, the IVCT is determined by the pressure at which the aortic valve opens./31/ Thus a higher aortic diastolic pressure would be expected to prolong the time necessary for the left ventricle to exceed this aortic pressure and thus will prolong the IVCT. However, since aortic diastolic pressure is usually maintained within a narrow range, the IVCT and PEP primarily reflect inverse changes in the LV dp/dt.

Because the IVCT sacrifices accuracy in those patients in whom an ACG cannot be obtained and in whom the onset of the initial components of M1 are difficult to determine, the easily and accurately measured PEP is now generally used to detect alterations in the duration of isovolumic contraction.

Left ventricular ejection period /35,36/ *(4-7 or 5-6, Figure 1)* /25/

The second component of total electromechanical systole, the left ventricular ejection time (LVET), represents the isotonic phase of left ventricular systole and in the final analysis is a function of the mean rate of myocardial fiber shortening. The most widely accepted measure of the LVET uses only the indirect carotid artery tracing, measuring from the beginning of the carotid upstroke (CA_u) to the trough of the incisura (CA_{In}). This method assumes that the time from the onset of LV ejection to the onset of CA_u is equal to the time from the end of LV ejection to the CA_{In}. This has been shown to be a valid assumption, and the LVET derived from an indirect carotid artery tracing agrees closely with an LVET similarly derived from an undamped central aortic pressure tracing./37/

Significance of left ventricular ejection period

The indirect assessment of LVET is another valuable adjunct in the bedside assessment of left ventricular performance. As shown in TABLE V, many factors can influence its duration. The heart rate is the most important determinant of LVET in normal subjects./38/ The next most important determinant of LVET is the stroke volume index (SVI) which explains the prolonged LVET in patients with aortic insufficiency (increased true SVI). The LVET is also prolonged in patients with aortic stenosis, but in these cases the prolongation is due to the associated reduction in velocity of myocardial contraction secondary to the excessive load placed on the left ventricle by the high outflow resistance. Paradoxical splitting of the

second heart sound in severe aortic stenosis or severe systemic hypertension may be explained by this prolongation of the LVET./39/ Because of the reduction in sympathetic nervous tone and myocardial "contractility" and the increase in aortic impedance with increasing age, the LVET increases in duration approximately 2.0 milliseconds per decade./40/

TABLE V

LEFT VENTRICULAR EJECTION PERIOD

Shortened by...	*Prolonged by...*	*Unaffected by...*
Tachycardia	Bradycardia	Chronic changes in aortic blood pressure
Congestive heart failure	↑ stroke volume	Left ventricular end-diastolic pressure
Left bundle branch block	↑ cardiac output	Extent of coronary artery disease
Acute myocardial infarct	Hypothyroidism	Respiration
↓ stroke volume	↑ age	Right bundle branch block
↓ cardiac output	↓ serum [Ca++]	
Inotropic interventions (digitalis, isoproterenol)	Amyl nitrite	
Hyperthyroidism	Aortic stenosis and insufficiency	
↑ serum [Ca++]	Acute marked aortic hypertension	
Passive head up tilting		
Pulsus alternans		

Patients in congestive heart failure exhibit a diminished LVET not only because of an associated reduction in SVI secondary to depressed myocardial function but also because of the delay in aortic valve opening caused by a prolonged IVCT occurring in the face of a stable total systolic duration. In patients with acute myocardial infarcts, the LVET is shortened primarily because of the associated reduction in myocardial "contractility" but also because of a reduced SVI secondary to associated ventricular asynergy, papillary muscle dysfunction, or altered left ventricular compliance. The LVET is, however, not well correlated with LV end-diastolic pressure or the extent of coronary arteriographic disease in patients with chronic coronary artery disease.

Finally, the dose dependent abbreviation of LVET caused by digitalis offers a potentially useful technique for assaying the effects of digitalis on left ventricular myocardium./41,42)

Protodiastole

Protodiastole is the brief interval between the end of LV ejection and the beginning of isometric relaxation. Since it is

usually calculated with the ejection period (LVET), it will not be considered further.

Isometric relaxation period *(6-8, Figure 1)* /43/

The isometric relaxation period (IRP) represents the time between the closure of the aortic valve and the opening of the mitral valve coincident with the commencement of diastole when the rapidly falling left ventricular pressure crosses the left atrial pressure. The time of closure of the aortic valve is measured on the phonocardiogram from the onset of the high frequency vibrations of the aortic component of the second heart sound (A2). The "O" point of the ACG is used to approximate the opening of the mitral valve although this point actually corresponds not with the mitral opening itself but rather with the direct hemodynamic consequences of the mitral opening. The "O" point follows the mitral opening by 5-30 milliseconds, but for the purposes of measurement of the IRP, this systematic error can be ignored.

Significance of the isometric relaxation period

Although the IRP is dependent on left atrial and aortic pressure as well as left ventricular pressure, it is the downslope of the LV pressure curve which is primarily responsible for the duration of the IRP. Either aortic or atrial pressure would have to move outside the physiologic range to appreciably change the IRP, if the LV pressure downslope remained constant.

The IRP may also be delayed by either an early closure of the aortic valve or by a delayed onset of ventricular filling. TABLE VI lists those influences which have been reported to alter the IRP. The delay in ventricular relaxation associated with aging has been attributed to diminished myocardial elasticity in the elderly./44/ Such a prolongation in the IRP may partially explain the reduced tolerance of tachycardia common in the elderly patient.

These alterations in the rate of ventricular relaxation appear to be determined at the cellular level primarily by the ability of the sacroplasmic reticulum to release and reaccumulate ionic calcium, the converse of excitation – contraction coupling./24/

TABLE VI

ISOMETRIC RELAXATION PERIOD

Shortened by . . .	*Prolonged by. . .*	*Unaffected by. . .*
Exercise-induced tachycardia Isoproterenol	Increasing age Digitalis	Atropine or pacing-induced tachycardia

Rapid inflow period *(8-9, Figure 1)*

As diastole is ushered in by AV valve opening, blood surges into the relaxed ventricle at a time when ventricular pressure is falling rapidly. Most of the ventricular filling is accomplished during this rapid inflow period which is measured on the ACG as the rapid filling wave (RFW). This RFW extends from the "O" point to the point where the subsequent steep rise merges into a slower filling wave. The peak of the RFW coincides with the moment when the intraventricular pressure reaches its lowest point and corresponds with both the early diastolic dip of the LV pressure tracing and with the third heart sound (S3) or protodiastolic gallop. This rapid inflow period is greatly diminished or absent in patients with significant mitral stenosis or pressure overload of the left ventricle but is accentuated in those with predominant mitral insufficiency or volume overload of the left ventricle.

Slow inflow period *(9-10 Figure 1)*

The slow inflow period or diastasis is defined by the slow filling wave (SFW) on the ACG and extends from the peak of the RFW to the onset of the "A" wave of the next cardiac cycle. This period is characterized by very little change in left ventricular volume and is that portion of diastole which is most compromised by an increasing heart rate.

Atrial systole *(10-2, Figure 1)*

This period represents the effects of left atrial contraction on left ventricular filling and is measured on the ACG from the onset of the "A" wave to the onset of the rapid systolic wave (ACG_U). Atrial systole contributes 15-25 percent of the total left ventricular diastolic volume at normal heart rates and even greater amounts at more rapid rates. The information

which may be obtained from an analysis of the "A" wave has been discussed under APEXCARDIOGRAM.

CONCLUSIONS

The measurement of systolic and diastolic time intervals can now be obtained from such noninvasive techniques as the simultaneous recording of the electrocardiogram, phonocardiogram, apexcardiogram and carotid arterial pulsation. This review has attempted to define these intervals in terms of the underlying cardiac events and to present the reported hemodynamic and clinical correlations afforded by such measurements. The most recent interest has been focused on determinations of certain systolic time intervals, particularly the PEP or IVCT and the LVET. In fact, the ratio of the PEP to the LVET (PEP/LVET) may offer the most promise for widespread acceptance and application./45/ This ratio does not require the use of the ACG, a technique which is often precluded in obese or heavily muscled patients or in patients with obstructive pulmonary disease. Further. this ratio remains within narrow limits in normal patients even when uncorrected for sex and heart rate yet incorporates and accentuates the information obtained from either the PEP or the LVET alone, since these intervals tend to vary inversely in the presence of myocardial dysfunction.

Impaired intrinsic contractile performance characteristics in either hypertrophied or failing myocardium are reflected in a reduced velocity of contraction for any given load (reduced "contractility") and in a reduced peak rate of left ventricular pressure rise during isovolumic contraction (reduced LV dp/dt). This deficient force development in early systole causes (1) a reduced rate of rise of intraventricular pressure throughout the PEP thus prolonging the PEP, and (2) an abbreviation of the subsequent LVET because the duration of total electromechanical systole is relatively constant. The PEP and LVET therefore are altered in opposite directions in the presence of impaired myocardial function.

An increased ratio (PEP/LVET) may suggest not only a diminished cardiac output or stroke volume but also provide a semiquantitative expression of the degree of flow impairment as well. A highly significant inverse correlation between PEP/LVET and the

LV ejection fraction as determined angiographically has been found even in the presence of valvular insufficiency./1,46/ Also, a significant positive correlation has been noted with the LV end-diastolic volume./46/ This ratio is reported to rise with increasing peripheral resistance, with beta-receptor blockade (propranolol), with the assumption of the upright position, or during peripheral pooling of blood with venous occlusive tourniquets. Left bundle branch block also increases the PEP/LVET whereas beta-receptor stimulation or inotropic interventions (digitalis, isoproterenol) diminish it.

This PEP/LVET ratio thus represents a composite expression of the isovolumic and isotonic phases of systole and will likely achieve more widespread application as these hemodynamic correlations are corroborated and extended.

These indirect graphic techniques as presently used in the measurement of systolic and diastolic time intervals provide the most sensitive and valid data when used in the serial evaluation of the individual patient. In this way, each patient may serve as his own control, and subtle changes in his time intervals may thus assume greater significance. Of particular interest are the changes induced in these indirect intervals in the individual patient following provocation with exercise /46-48/ right atrial pacing /49/, or pharmacologic intervention. Similarly, small serial changes in the systolic time intervals such as an increasing PEP/LVET may provide, for example, an early warning of incipient myocardial failure in a patient suffering with an acute myocardial infarction.

Such techniques will nevertheless remain inexact, partly because of the continued difficulty relating the derived time intervals to precise intracardiac events, during which the coupling with the thoracic wall is critical but undetermined. Their measurement will also remain imprecise and potentially misleading if certain often interdependent variables are not controlled or critically considered. But despite our present inability to accurately quantitate left ventricular function using externally derived time measurements, estimates of many of these parameters of myocardial performance are now possible and the continued application of these noninvasive techniques should be encouraged.

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APPENDIX *Normal Values* Cardiac Time Intervals - McConahay*

Total electromechanical systole [Q–A2]

546 2.1 HR ± 14 msec [1]
490 -1.7 HR ± 17 msec [2]

Pre-ejection period [(Q–A2)–(CA_u–CA_{In})]

131 -0.4 HR ± 13 msec [1]
111–0.3 HR ± 15 msec [2]

Electromechanical lag [Q - ACG_u]

22 ± 9.8 msec (0–50) [3]

Isovolumic contraction time [(ACG_u - CA_u)— (A2 - CA_{In})]

70.9 ± 15.8 msec (40-90) [4]
50.2 ± 8.6 msec (30-65) [5]
41 ± 6 msec [6]
52–0.2 HR ± 15 msec [2]

Left ventricular ejection time [CA_u–CA_{in}]

413 1.7 HR ± 10 msec [1]
416 1.56 HR ± 19.1 msec [7]
380 1.3 HR ± 19 msec [2]
376 - 1.2 HR ± 12 msec [8]

Isometric relaxation time [A2–O]

90 -0.34 HR ± 14 msec (40-100) [3]
103 –22 msec [9]

Rapid inflow period [O–F]

99.8 ± 14.2 msec (80-120) [3]

Ratio Pre-ejection period to left ventricular ejection time (PEP/LVET)

0.345 ± 0.036 [10]

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*Recommended measurements in parentheses. HR = heart rate, Q = Q-wave, A2 = initial high frequency vibrations of aortic component of second heart sound. CA_u = upstroke [point of origin of the carotid artery upstroke] CA_{In} = carotid incisura [point separating systolic and diastolic phases of carotid pulse] ACG_u = upstroke of apexcardiogram. O = nadir. F = point where rapid filling wave merges into slow filling wave.

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MYOCARDIAL REVASCULARIZATION

LTC John P. Nagle, MC

Coronary artery disease is enjoying a widespread epidemic in the United States much to the chagrin of physiaians who have for years sought a solution to this problem. Recent epidemiologic studies tell us that approximately one million people will sustain an acute myocardial infarct in 1971 out of a population of three to six million people with symptomatic coronary artery disease./1,2/ In addition, there is a large population estimated at four to five million, with asymptomatic atherosclerosis that has potential for becoming symptomatic./3/ Atherosclerosis is a pathologic process that begins early as attested by the impressive studies in people dying of accidental death or death in time of war./4,5/ Seventy-seven percent of young Americans killed in the Korean war (mean age of 22) had gross pathological evidence of atherosclerosis. Of these, 12.3 percent had significant stenosis or occlusion already present. This frequency increases with age so that by age 50 to 60 years pathologic changes of atherosclerosis, although not necessarily symptomatic, are almost universal in the United States.

With these impressive facts in mind, it is no wonder that a tremendous amount of effort is being put forth to define the etiology and institute preventive measures for this ubiquitous disease. This is where the impetus should be placed! However, there remains a large number of patients who already have acquired significant coronary atherosclerosis. It is in these patients that medical and surgical forms of therapy are important. This paper will confine its discussion to the surgical approaches to myocardial revascularization and their present clinical status.

Pathologic and Coronary Arteriographic Aspects of Coronary Artery Disease (CAD) as They Relate to Surgical Approaches

The surgeon approaching a person with coronary disease must have a knowledge of what the usual pathological findings are as well as the angiographic findings in each particular case. Only with this knowledge can he properly formulate a surgical plan preoperatively and know what to expect at surgery.

Pathologic correlates in coronary disease received impetus when Schlesinger/6/ developed a method of injecting coronary arteries with lead agar at necropsy. Initial clinicopathologic studies concluded that occlusion of one or more major coronary arteries was the underlying cause of angina pectoris. It was further emphasized (and since that time it has been repeatedly confirmed) that (1) the atherosclerotic process occurred more frequently and was more severe in the proximal third of the vessels and (2) occlusions were usually less than five millimeters in length. The atherosclerotic process involves primarily the epicardial coronaries and not those extending into the myocardium. Collaterals do not form in normal hearts but are seen only with varying degrees of coronary stenosis or occlusions./7-9/ However, even the early pathologic studies frequently demonstrated diffuse disease extending beyond the middle third of the vessel and early direct approaches to coronary surgery were discouraged by extension of the disease down to vessels two to three millimeters in diameter. Recently, Vineberg/10/ has shown that 49 percent of hearts studied with coronary artery disease have disease in the distal five centimeters of coronary trunks and branches.

With the recent development of microvascular surgical techniques (allowing anastomosis of vessels at the one to two millimeter size) a second look at the gross and micropathology is being taken. Thus, Green et al /11/ dissected 50 fresh postmortem arteriosclerotic hearts and found that in 49 of 50 cases at the coronary arterial external diameter of 1.5 millimeters and beyond, the lumen of the vessel appeared normal. On the contrary, they found that most segments at a diameter of 2.0 millimeters were not suitable for receiving a vascular

anastomosis. Recently, Berger /12/ has reported a study of 300 hearts with anatomic assessment of operability by the direct approach. An operable lesion was defined as (1) proximal stenosis of greater than 50 percent, (2) distal artery suitable for anastomoses, i.e. absence of significant disease and circumference greater than 4.0 millimeters and (3) adequate runoff without distal stenosis. He found that 117 (39 percent) had single vessel disease, 99 (33 per cent) had double, and 84 (28 percent) had triple vessel disease. Eighty-five percent of the single vessel lesions were operable. With two vessel disease, 28.3 percent were operable for one lesion, 63.6 percent for both lesions and 8.1 percent were inoperable. With three vessel disease, 24 percent were operable for one, 40 percent for two, 25.3 percent for three vessels and 10.6 percent were inoperable. The 900 vessels of 300 hearts had 570 lesions and 406 (70.5 percent) were operable. The site of operability was 9.3 percent in the proximal, 60.1 percent in the mid-third, and 30.4 percent in the distal third of the involved coronary arteries. So, pathologic studies demonstrate an operability rate (by direct bypass surgery) of 70 to 95 percent depending on the size of the artery the surgeon can anastomose; the smaller the vessel the higher the operability rate.

With the demonstration by Sones and Shirey /13/ in 1959, that selective coronary arteriography could be done safely with low risk and reliable high quality angiograms, the field of clinical-anatomic correlation in coronary heart disease was opened. For the first time there could be a rational surgical approach based on anatomic knowledge and there could be a realistic anatomic evaluation postoperatively. Concerning expected findings with antemortem angiogram, Proudfit et al /14-16/ reported on the clinical correlates of 1000 patients who had coronary arteriograms. In 37 percent of the group, no significant obstruction was found although almost the entire group were suspected at some time of having coronary disease. In 300 patients thought to have noncoronary symptoms, 17 percent had significantly stenotic lesions. Typical angina pectoris had 95 percent correlation with significant arterial lesions and diagnostic Q waves of myocardial infarction on electrocardiograms (ECG) and had a 99 percent correlation with severe arteriographic patterns. Rest pain, "coronary failure" and "atypical angina" showed decreasing correlations for significant lesions (79, 78, and 65 percent respectively). In 627 of the patients the obstructing lesions exceeded 30 percent with the left anterior descending (82.5 percent), right

(72.9 percent), circumflex (66.0 percent), and left main (41.5 percent) coronary arteries involved. Complete occlusions were more common in the right coronary whereas 50 to 90+ percent obstruction was most frequent in the left anterior descending artery. More than 75% of symptomatic patients had 90 percent or more obstruction of at least one vessel and more than 50 percent had total occlusions of one or more vessels. Predominantly single vessel involvement was seen in 21 percent. Multiple-vessel involvement was common. The average number of arteries affected by lesions exceeding 30 percent of the lumen was 2.3, the average number of arteries 75 percent (or more) occluded.

Dietrich et al /17/ reviewed 313 patients with angina pectoris. Significant disease (greater than 75 percent stenosis of at least one major vessel) occurred in 270 of 313 (87 percent) patients. Significant (75 percent or greater) obstruction occurred in single vessels in 58 of 270 (23 percent); double in 110 of 270 (40 percent); triple in 78 of 270 (29 percent); and quadruple in 24 of 270 (9 percent). The distribution in 191 arterial occlusions was — right coronary in 101 of 191 (53 percent); anterior descending in 64 of 191 (33 percent); and circumflex in 26 of 191 (14 percent). It is interesting that complete occlusion of the left main coronary was not seen in this or the studies by Proudfit et al /14-16/; therefore, one could surmise that this is generally a fatal lesion.

An additional point worthy of further study is the subject of progression on serial angiography. Not many studies have dealt with this specifically, but in studying postoperative results it has been shown that over a year's period one can be expected to show significant progression of their arteriosclerotic process. Radiographic techniques are not infallible and surgical experience has consistently demonstrated more disease than expected angiographically.

Pathology and angiography is the approach which best describes the disease that faces the surgeon in his attempts at revascularization.

SURGICAL PROCEDURES

It must be pointed out at the offset that any attempts at revascularization are, at the present time, still in the experimental stage. Numberous procedures have been described

and attempted in humans. The road to surgical treatment for coronary heart disease is littered with the wrecks of operations whose supposed benefits lay largely in the enthusiasm of their originators. In addition, it is important to emphasize that any such operation, in addition to being experimental, is only palliative and not curative as some patients are led to believe.

TABLE I will serve as a guide so that one may get an idea of the types of operations devised to improve myocardial blood supply.

The majority of these procedures have been abandoned because of either unimpressive results or high mortality rates. At present the most commonly employed technique is the reversed saphenous vein aortocoronary bypass graft which has gained increasing enthusiasm over the past three years. There are centers still employing the indirect method of systemic artery implant (usually internal mammary) either alone or in combination with the saphenous vein bypass technique. Less frequently used are gas endarterectomy, local endarterectomy, and internal mammary to coronary artery anastomosis. The present surgical techniques and postoperative results will be briefly described.

INDIRECT REVASCULARIZATION BY INTERNAL MAMARY ARTERY IMPLANT PROCEDURES

Figure 1.

In 1946, Vineberg /18/ reported that a bleeding internal mammary artery implanted into a tunnel in the wall of the left ventricle would remain patent and develop a variable amount of collateral circulation. About 75 percent of Vineberg's experimental implants remained open. In 1950, Vineberg first employed this operation in man and he has continued to be its foremost proponent./19/

Several modifications of the original procedure have evolved. In the original operation, the internal mammary was dissected out as a naked vessel. This proved very tedious. In 1962 a technique employing a pedicle that contained the internal mammary artery, its vein and interconnecting communications as well as muscle, fascia, fat and lymphatic tissue was tried. This proved bulky, required considerably larger tunnel and resulted in increased mortality. Finally, this was modified to use the pedicle down to the myocardial tunnel and then to use the naked vessel in the tunnel./20/

TABLE I

PRODUCTION OF NEW ARTERIAL SUPPLY*

Production of Adhesive Pericarditis

Mechanical Abrasion: Beck, 1935

Installation or Insufflation of Irritating Substance

Dakin's solution: Beck, 1929
Asbestos powder: Beck, Schlidt and Stanton, 1943
Sodium morrhuate, *Lionile* ® carborundum: Hembecker, Barton, Slome, 1939
Talc: Thompson, 1939
Phenol and talc, Harken, 1955

Production of Venous Stasis or Reversal of Coronary Circulation

Occlusion of Coronary Sinus: Robertson, 1934, Gross, Bleus, 1935; Greg, Dewald, 1938; Fauteux, 1937; Beck, Mako, 1941

Arterialization of the Reversed Coronary Circulation: Roberts, 1934; Beck, 1948

Indirect Methods of Improving the Blood Supply of the Heart

Operation of the Sympathetic Nervous System

Synpathectomy (ganglionectomy): Jonneko, 1916; Danielopoler, 1924, Langley, 1924, Leriche, 1931; Coffey, 1923; White, 1957
Resection of Preaortic cardiac plexus: Fauteux, 1941; Arnulf, 1939
Posterior rhisotomy: White, 1957

Use of Flaps of Pedicle Grafts

Mediastinal fat and retrosternal tissues. Beck, 1935
Skeletal muscle Beck, 1935
Pedicled grafts of skin and subcutaneous tissues: Neuman and Von Vedel, 1952
Omentum: O'Shaughnessey, 1936
Lung. Lezuus, 1937, Carter, 1949
Jejunum Key, 1954
Stomach: Mines, Hipp, 1960

Transplantation of arterial vessel or graft into myocardium

Internal mammary. Vineberg, 1946
Subclavian artery: Luguag, 1958
Splenic artery: Bloomer, 1960
Left ventricular chamber. Euria, 1956
Left auricular chamber: Euria, 1956
Thoracic aorta graft: Smith, 1957

Direct Surgical Approach to Coronary Artery Disease

Endarterectomy or Intimectomy: Pratt, 1959; Absolon, 1956; May, 1957; Bailey, 1957; Longmire, 1958
Substitution of graft for occluded segment: Murray, 1952
Direct anastomosis of other vessels to coronary arteries: Murray, 1954; Absolon, 1956, Thal, 1956; Moore and Rilieu, 1958
Resection of infarcted myocardium: Marray, 1947

* *From* Nichols HT, Likoff W, Mozer I: *Coronary Heart Research* New York: Grune & Stratton, 1963. p 446

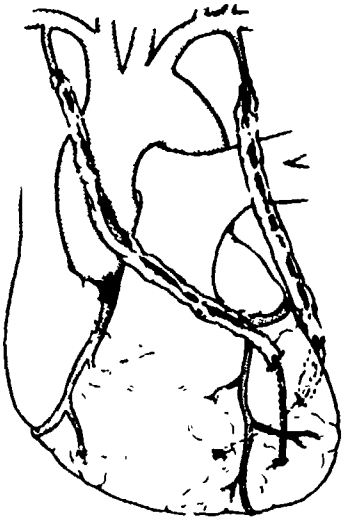

Fig. 1. INDIRECT MYOCARDIAL REVASCULARIZATION, with right internal mammary artery implanted in left ventricle, [illegible]ing diagonal branch of left anterior descending artery; implanted left internal mammary artery in posterior wall of left ventricle.

After the development of selective coronary arteriography it was demonstrated that the internal mammary of a patient operated on by Vineberg some years before had developed anastomoses with the left coronary system. Then great interest and enthusiasm developed for the procedure and thousands of internal mammary implants or variations on the theme have been performed and much has been learned.

A collective review by Breuer and Warren /21/ in 1965 stated that 50-80 percent of implants had been reported to be patent. The majority of the reports subsequently have indicated a higher patency rate (approximately 90 percent). Patency rate however, does not equal rate of angiographic evidence of anastomoses with existing coronary arteries. The reported rate of anastomoses has been about 50 percent but may be higher if implants are into areas of "demand"./22/

Immediately following surgery in humans, flow meter studies generally show the range of blood flow to be 5-7 milliliters per minute. Amazingly enough, the vessels remain patent despite these low flows and hematoma does not form from the bleeding vessel in the myocardium. Patency is apparently related to a number of factors which include (1) a to-and-fro motion of

blood in the implant (systolic pressures in the implant in the tunnel are higher than aortic pressure and flow is retrograde from internal mammary to aorta in systole and vice versa in diastole)/23/; (2) the myocardial simusoids capable of absorbing the flow; (3) mechanical defibrination and (4) regional ischemia. This latter aspect, that of regional ischemia, is apparently the most important factor governing formation of collaterals. This has been demonstrated both experimentally and clinically and is referred to as "demand". This pattern of "demand" can be established preoperatively by angiographic demonstration of intercoronary collateral circulation, indicating that regional ischemia is present. Depending on demand and formation of internal mammary to coronary anastomoses, the flow gradually increases over the next three to six months, i.e. this has been the usual time it takes to demonstrate significant anastomoses angiographically. Actual flow studies in humans have been few in number but in animals flows up to 40-65 milliliters per minute have been recorded./22/

In the large experience at the Cleveland Clinic no instance of an internal mammary artery has been seen forming communications with vessels remote from the site of implantation./24/ That is to say, an anterior left ventricular implant has not been seen to anastomose with the vessels supplying the posterior wall. Because coronary heart disease is so frequently a disease of multiple vessels, various types of procedures have been devised to revascularize the areas associated with arteriographic evidence of significant obstructive disease. These include implantation of both internal mammaries, retrograde implantation of the left mammary artery, a saphenous vein autograft, the gastroepiploic artery, intercostal arteries, and the splenic artery. The objective with all techniques has been to implant one artery into the region of the anterior wall and anterior descending and another into the lateral diaphragmatic portions of the left ventricle near the tributaries of the circumflex and posterior descending coronary arteries.

Immediate operative mortality is between two and five percent with a five to ten percent late mortality in the first two years following surgery (this is less than the expected mortality of a similar group of patients treated medically)* Improvement to varying degrees in angina pectoris can be anticipated in 60-75 percent of patients./22/

*These percentages are not from a controlled series.

Postoperative assessment other than subjective improvement in angina has been difficult. Simple angiographic patency and even formation of collaterals does not necessarily mean that significant blood flow is being supplied by these implants. Postoperative improvement in hemodynamics has been reported in some series and not in others./22, 25/ Improved myocardial metabolism as measured by lactate studies have been used by some authors as evidence of improved flow to ischemic areas /26/, but it is not certain that infarction of a previous ischemic area is not also an explanation for this improvement. Coronary flow studies are experimental themselves and have not been done in a significant number of cases to establish confidence in numbers obtained by these methods. The problem of regional coronary flow (i.e. whether or not the measured blood flow is actually to the ischemic areas and not bypassing them) has not been solved. Stress testing, pre and postoperatively, may be a better estimate of significantly improved flow than simple patency./27/ However, the response to stress testing is nonspecific and variable in and of itself.

Perhaps the most impressive information concerning the ability of implants to establish significant flow in certain individuals is Vineberg's remarkable collection /28/ of seven patients in whom the only artery open in the heart was the implant placed there $3\frac{1}{2}$-$17\frac{1}{2}$ years before. All the patients' own coronary arteries had slowly occluded. There has been a lot of controversy among both cardiologists and surgeons as to whether or not indirect procedures have any value at all. At least part of this stems from the fact that it usually takes three to six months to establish what seems to be at times insignificant amounts of flow by a procedure that is undoubtedly itself causing some degree of direct myocardial damage (although this latter point is not considered to be important by some authors). Because of these factors as well as others, it is not surprising that many surgeons have almost completely abandoned the indirect procedures in favor of direct surgical approaches where immediate results are often dramatic.

AORTO-CORONARY SAPHENOUS VEIN BYPASS
Figure 2.

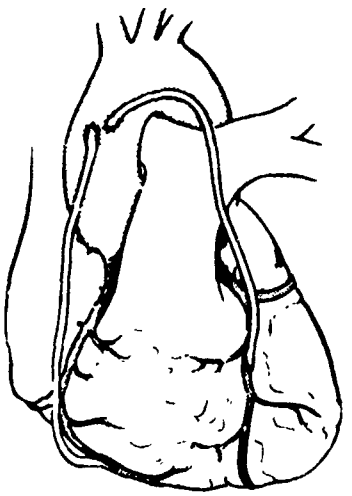

Fig. 2. DIRECT MYOCARDIAL REVASCULARIZATION by means of saphenous vein bypass grafts to distal right coronary artery (posterior descending) and left anterior descending artery.

Over the past three years there has been rapid and exciting development of various procedures employing saphenous vein bypass of obstructive coronary lesions. The saphenous vein for bypass grafting was first widely employed by Favaloro et al /29/ at the Cleveland Clinic. Initially, this was used only for short segmental obstruction of the proximal right coronary, often by resecting the disease segment and interposing the vein graft. With experience, longer segments were bypassed directly from the aorta to the coronary distal to obstruction./39/ Multiple centers have now gained large experience using the coronary saphenous vein bypass. What has been learned in the three short years since its beginning can be summarized as follows:

The procedure appears to be widely applicable to a large number of patients with coronary artery disease and has been accomplished with a 5-15 percent operative mortality rate./30/

Vascular grafts can be accomplished to small vessels (internal diameter as small as 1.0-3.0 millimeters)./31

Subjective and objective improvement is effective almost immediately following establishment of flow distal to obstruction.

Substantial improvement of dysynergic motion of the left ventricle has been noted when this is related to ischemia and not to a previous scar./32/

Relatively soon after surgery, 10-20 percent of grafts will not remain patent and this seems to be highly likely if initial flows established are less than 25 cc/min and not responsive to papaverine injected via the graft which is said to be related to poor runoff distal to the anastomoses and not to stenosis at the anastomoses in the majority of cases./33/

A small but definite incidence of late occlusion of the graft is beginning to creep into the literature although not enough experience or followup has been gained at the present time. This late occlusion problem is, at least in some, due to a subintimal fibroplastic process that is not atherosclerotic in nature and its cause is presently unknown. It may occur as early as two to three months following the procedure./34/

These are but a few of the highlights in this exciting new field. Already it has gained wide acceptance as the surgical procedure of choice in the great majority of patients with symptomatic coronary disease. Bypass grafts have usually been performed on cardiopulmonary bypass with electrical fibrillation or ice arrest so that the anastomoses can be done on a quiet heart./35/ Others have performed the anastomoses in the beating heart. Usually the graft is placed distal to the furthest site of disease so that the runoff is into a normal arterial bed. When one deals with the right coronary artery this often means going to the back of the heart near the origin of the posterior descending artery; with the left anterior descending, one frequently must go down near the apex of the heart where the vessel is often only 1.0 to 3.0 millimiters in diameter; and with the circumflex, one finds the anastomosis is even more difficult to form on the posterior aspect of the heart. Despite these seemingly formidable tasks, surgeons have

have found that these anastomoses can be made and have performed multiple (two, three, and four) grafts in increasing numbers./36/ At Milwaukee they are performing multiple vein grafts in approximately 70 percent of those who come to surgery and have had only a small increased risk from surgery.

As stated before, this bypass procedure has been performed in conjunction with the indirect procedure of internal mammary implant. Most of the series indicate this is being done less and less frequently. It would seem appropriate to use an implant in areas with angiographic evidence of "demand" but in whom bypass graft cannot be performed.

The exact place in coronary surgical procedures the bypass will take is not known at present because we need still to determine the natural history of these grafts. In the distal extremities, venous bypass to small arteries, such as the dorsalis pedis, were plagued by 50 percent or greater occlusion rates. However, vein grafts in large peripheral vessels have been very successful with excellent long-term patency and freedom from aneurysm formation./37/ In some grafts an unknown number are prone to an excessive subintimal fibroproliferative process. Whether they will also develop atherosclerosis is unknown.

CORONARY GAS ENDARTERECTOMY

Figure 5

Early attempts at direct intervention employing standard endarterectomy and patch graft angioplasty for local lesions achieved only limited application either because of high mortality rates or failure to achieve long term patency. At least some of the problems resulted from incomplete "cleanout of diffusely diseased vessels, failure to reopen side branches ("snow plow" effect) with resultant impaired runoff and high mortality when operating on the left coronary artery.

Coronary gas endarterectomy was described in 1967 and shortly thereafter was overshadowed by the advent of saphenous vein bypass. However, some 75 cases have been performed in humans with gratifying results./38/ Again, these numbers are small and suffer from lack of followup over a significant period.

The procedure is generally done under partial cardiopulmonary bypass and is begun by using a [illegible]-gauge needle for introduction of carbon dioxide subadventitially, along the full

length of the artery and major branches with special spatulas. Either one or two arteriotomies are performed to extract the specimen.

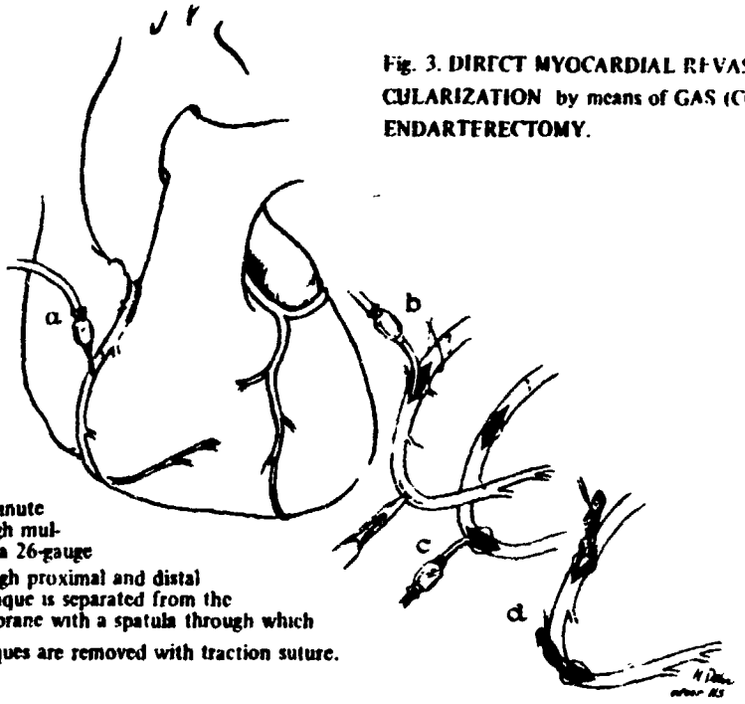

Fig. 3. DIRECT MYOCARDIAL REVASCULARIZATION by means of GAS (CO_2) ENDARTERECTOMY.

a CO_2 is injected at a flow of 15 liters/minute subadventially through multiple punctures with a 26-gauge needle. *b-c*, through proximal and distal arteriotomies, the plaque is separated from the external elastic membrane with a spatula through which CO_2 flows. *d* plaques are removed with traction suture.

Robinson et al /39/, reporting on 14 patients, demonstrated patency in nine of ten restudied. In two of these it had been longer than a year postoperative. All had severe three-vessel disease with either complete occlusion or diffuse disease of the right coronary. Dramatic retrograde filling of the left coronary via the reopened right coronary was seen in five patients. Dietrich et al /40/ have reported 40 cases with five deaths and two late closures. Urschel et al /41/ have performed 20 gas endarterectomies with three deaths and four early and one late closure.

Although this procedure is still in its experimental phase, it may offer another approach to the surgical treatment to coronary heart disease. At present it has only been applied clinically to the diffusely diseased or totally occluded right coronary.

INTERNAL MAMMARY TO CORONARY ARTERY ANASTOMOSIS

The procedure of anastomosing the internal mammary to the left anterior descending coronary has been employed by a few surgeons with a fair degree of success./42/ This procedure utilizes a normal artery and obviates the proximal anastomoses. Microvascular surgical techniques have been used employing the operating microscope. A high patency rate has been achieved in those patients restudied. Yet to be answered is the size of flow which can be achieved and whether long term patency and freedom from the atherosclerotic process will be obtained.

SELECTION OF PATIENTS FOR STUDY AND SURGERY

At present the subject of selecting patients for study and ultimate surgery is in a tremendous state of flux. Previously, most conservative cardiologists would study for surgery only those patients with intractible angina pectoris not ammenable to "maximal" medical management. A large heart, congestive failure, and previous myocardial infarcts were variably considered contraindications or at least poor risks for surgery.

With the advent of saphenous vein bypass and its often dramatic immediate results, the pendulum has swung the other way. In fact, in some large centers, the mere possibility of coronary artery disease is considered an indication for study and surgery if a significant bypassable lesion is found. In some centers 95+ percent of patients considered for surgery are operated on.

Obviously, there is some middle-of-the-road approach that will eventually dictate our indications. This will depend on a number of things including further knowledge of the natural history of certain clinical angiographic correlates. For instance, it is already suspected that angiographic evidence of severe stenosis of the main or proximal left anterior descending coronary has a poor prognosis, and in some centers such patients are operated on in a semi-emergent fashion when the lesion has manifest itself. Revascularization attempts following or during acute myocardial infarct or preinfarction angina is commented upon in another paper in this symposium (pages *353 ff*).

In addition, it must be reiterated that all coronary surgery is still experimental and awaits long term followup for proof of benefit.

In the meantime, each physician will have to formulate his own indications for study and surgery based on his own experience with diagnostic studies and surgery; nether are without risk.

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Medical treatment consists of pouring drugs of which we know nothing into a patient of whom we know less.

— VOLTAIRE

It should be the life-long labour of all physicians to make this statement increasingly false. — *M.D.C*

SURGICALLY TREATABLE COMPLICATIONS OF ACUTE MYOCARDIAL INFARCTION

MAJ Bruce H. Brundage, MC

The treatment of arteriosclerotic heart disease has been the unchallenged domain of the internist until the last decade. With the development of effective revascularization techniques, the results of which are treated in another article in this issue, the surgeon has begun to play an important role in the treatment of coronary artery disease. This discussion will deal with a less frequent but important role played by our surgical colleagues in treating certain complications of acute myocardial infarction often unresponsive to medical management.

Mitral Insufficiency

The onset of a mitral insufficiency murmur following acute myocardial infarction is common, but the internist must recognize when this sign heralds an impending disaster that only surgical correction will prevent. The most critical clinical situation signaled by this murmur is rupture of a papillary muscle. This rare complication occurs more frequently with posterior wall, rather than anterior wall, infarction because rupture of the posteromedial papillary muscle occurs twice as often as rupture of the anterolateral muscle. /1,2/ The murmur is usually harsh and is best heard at the apex; however, at times it may be soft. An associated thrill is uncommon /3/ and the absence of this physical finding is an important differential diagnostic point which is discussed in more detail on page 356. Apical diastolic sounds are common and, in one case, angiography demonstrated mid-diastolic mitral regurgitation. This angiographic finding is similar to that seen in severe aortic insufficiency and is thought to be one of the mechanisms for the Austin-Flint murmur. Since rupture of a papillary muscle results in a completely unsupported mitral commissure, wide open mitral insufficiency results. Rapid clinical deterioration in the form of pulmonary edema quickly follows the onset of the murmur. Seventy percent of cases are dead within 24 hours and eight-five percent in two months./2/ Emergency open heart

surgery is the only real chance for survival. Prosthetic replacement of the mitral valve following diagnostic confirmation by cardiac catheterization is the treatment of choice. /1,2/

While rupture of the papillary muscle following infarction is rare, involvement of the papillary muscle with infarction is not. In one autopsy series, 25 percent of the hearts had gross scarring or fresh infarction of the papillary muscle. The anterolateral muscle was involved in 79 percent and the posterolateral in 58 percent./4/ Even if the papillary muscle itself is not infarcted but the left ventricular wall at its base has been rendered dyskinetic or akinetic by acute ischemic injury, papillary muscle dysfunction may result. In either case, mitral insufficiency may result. The onset of the murmur may be abrupt or insidious and usually occurs four to six days after the myocardial infarct./1/ The murmur is usually holosystolic but occasionally it is ejection in quality and may be confused with aortic stenosis. An atrial sound (S_4) indicates a fairly normal sized atrium, forcefully contracting, and favors recent onset of the mitral insufficiency. Most cases respond well to medical management; occasionally, however, a refractory case will require surgical intervention. Before surgery, cardiac catheterization should be performed to quantitate the severity of the mitral insufficiency, evaluate the contractility of the left ventricle, and rule out an associated left ventricular aneurysm. Whenever possible, surgery should be delayed 6 to 12 months so that the injured myocardium may heal adequately./1/ Annuloplasty, plication and prosthetic replacement of the valve have all been used with some success./1/

Ventricular Aneuryms

Ventricular aneurysms have been demonstrated in 3.5 to 35 percent of patients with a previous transmural infarction. Ofter ventricular aneurysms do not have functional or prognostic significance, but if the aneurysm occupies 20 to 25 percent of the total surface area of the left ventricle, the amount of fiber-shortening required for adequate cardiac output is exceeded and failure ensues./1/

Aneurysms have been described as dyskinetic, akinetic, and hypokinetic. Dyskinesia of the ventricular wall implies a systolic expansion of the aneurysm, akinesia indicates no wall movement with systole, and hypokinesia denotes an impaired movement of the wall. Regardless of the particular dynamics of the aneurysm,

the wall. Regardless of the particular dynamics of the aneurysm, its presence means that a portion of the contractile force from the remaining viable myocardium is diverted from aortic ejection.

Hypertension and inadequate bed rest following acute myocardial infarction have been suggested as contributory factors in the development of aneurysms, but recent reports do not substantiate this./5/ Formation is determined primarily by the amount of local wall thickness actually necrosed and to a lesser extent by the total surface area involved in the infarction.

Clinically, a left ventricular aneurysm may be suspected if an ectopic precordial systolic pulsation is appreciated. The heart sounds may be diminished and gallops are often present. The electrocardiogram will show persistent ST segment elevation in 60 percent of the cases. The heart contour on chest roentgenogram may suggest the diagnosis, but fluoroscopy is more helpful by detecting paradoxical pulsation and linear calcification. Unfortunately the routine chest x-ray and fluoroscopy may be unrevealing and ventriculography remains the definitive diagnostic procedure.

Intractable failure is the most common indication for surgery, however, occasionally aneurysms will cause recurrent ventricular tachyarrhythmias which respond only to surgical removal. Infrequently, recurrent systemic embolization is an indication for aneurysmectomy. Emboli are the cause of death in nine percent of patients with LV aneurysms and at autopsy 38 percent have evidence of systemic emboli.

The goal of surgery is to remove or plicate the noncontractile or paradoxically pulsating area. Left ventricular efficiency is improved by diminishing left ventricular dimensions (LaPlace's Law) or by eliminating an expansile pouch which robs stroke volume like an insufficient mitral valve. The surgical mortality for these procedures has been reported to be from 7.9 to 32 percent./6,7/

Post-infarction Interventricular Septal Defect

Rupture of a necrotic ventricular septum is another complication of myocardial infarction that frequently requires surgical

intervention. This accounts for one to two percent of deaths due to infarction. Rupture usually occurs within two weeks of the infarct./1,8,9/ Concomitant infarction of the left ventricular free wall is always present when rupture occurs./8/ James /10/ states that perforation usually is the consequence of occlusions of both the anterior and posterior descending coronary arteries. Perforation results only then because the highly developed anastomosis between the two vessels negates extensive necrosis of the septum when only one is obstructed. Hypertension, early physical activity, and size of infarct have been implicated as other possible etiologic factors.

Clinically, perforation is heralded by the sudden onset of a harsh crescendo-decresendo pansystolic murmur loudest at the fourth left sternal edge, apex, or in between./1,8,9/ Rupture occurs frequently at the apex, explaining the more common apical location of the murmur than seen with congenital ventricular septal defects. The murmur is accompanied by a thrill in more than half the cases. The onset of the murmur is usually accompanied by rapid clinical deterioration manifested as shock or congestive failure. The failure is atypical for acute infarction because right-sided failure without associated pulmonary edema is common. Twenty-four percent of the patients die in the first day and 60 to 70 percent in the first two weeks. The extremely critical state of these patients often results in prolonged monitoring with intravascular and bladder catheters which has resulted in bacterial endocarditis of the ruptured septum./11/

The primary difficulty in diagnosis is differentiating this from a ruptured papillary muscle. The physical findings can be the same for both groups. However, a thrill and a predominate, right-sided failure with peripheral edema favor septal perforation. Selzer et al /8/ believe the only valid differential point is that patients who develop loud systolic murmurs after myocardial infarction and who survive the initial two days are much more likely to have septal perforation than papillary muscle rupture./8/ Electrocardiographic evidence of conduction defects have been reported to be frequently associated with septal perforation /3/ but others refute this diagnostic point./8/ Accurate diagnosis makes cardiac catheterization mandatory./1,8,9/ Right heart catheterization will detect the presence of a right to left shunt. Often pulmonary blood flow is three to four times greater than systemic blood flow. A high incidence of ventricular aneurysms has been reported in association with septal rupture /8,9/ and so, if

the patient's condition allows, left heart catheterization with ventriculography should be performed.

Medical treatment has resulted in an 89 percent mortality and so surgery is often indicated. It is preferable to wait six weeks to six months before surgery is performed to allow fibrous healing around the perforation which insures better repair./1,8,9/ However, in the acute stage, surgery may be life-saving if shock or severe failure are unresponsive to medical management. Surgery carries a rather high mortality (27 percent); however, half of the operated patients have survived up to 7½ years./9/

Cardiogenic Shock

The medical treatment of cardiogenic shock has consistently resulted in an 80 to 85 percent mortality rate. New ideas about treatment must be sought if these statistics are to be improved. One area that is being actively investigated is infarctectomy. The principle of this form of therapy is -— an infarct is in essence an acute ventricular aneurysm resulting in the same hemodynamic effects as a chronic aneurysm. Its removal in cardiogenic shock may improve cardiac output enough to tip the balance in favor of recovery.

A number of experimental studies have been carried out in dogs demonstrating the beneficial effects on hemodynamics and survival following removal of large acute infarcts./12-14/ It has been shown, however, these these animals will not survive excision of greater than 30 percent of the left ventricular free wall. An interesting study in calves demonstrated that 100 percent of control animals died following anterior descending artery ligation while 50 percent of similar animals survived after infarctectomy./15/ There have been a few reports of infarctectomy in humans with indications of some promise for this procedure./6,7,12,16/ In two instances, the acute infarct occurred as a complication of prosthetic valve replacement, and the patient could not be brought off cardiopulmonary bypass until the infarctectomy had been performed./12/ Three cases of left ventricular aneurysm were complicated by an acute infarction which resulted in unresponsive cardiogenic shock. They were successfully managed by combined aneurysmectomy and infarctectomy./7/ Griffith /12/ has suggested that any case of cardiogenic shock unresponsive to three hours of medical therapy should be considered a candidate for infarctectomy.

Miscellaneous Conditions

There are several other instances where surgery may rarely be indicated for treating a complication of acute myocardial infarction. One is permanent complete heart block. While heart block occurs in approximately 10 percent of acute infarcts it usually abates within two weeks. Should it persist beyond three weeks a permanent pacemaker is indicated. This need occured only once in a series of 300 cases of acute myocardial infarct./1/

Cardiac rupture occurs in 8.6 percent of fatal infarcts but the majority of patients die suddenly or are found dead, allowing no time for surgical intervention./17/ On occasion, however, the symptoms of severe chest pain and the signs of cardiac tamponade suggest the diagnosis which can be confirmed by pericardiocentesis. If this occurs, there may be up to twelve hours before death during which time immediate operative intervention might save the patient. The diagnosis should be suspect in elderly hypertensive patients during the first two weeks following an acute infarct.

Finally, systemic emboli, a rare complication of myocardial infarct since the widespread use of anticoagulants may require surgical treatment. With peripheral emboli resulting in acutely ischemic extremities, the use of Fogerty catheters in these vessels has at times been life-saving./18/

Aortocoronary bypass has been tried in the treatment of acute infarction. Occasionally a patient with an obvious acute myocardial infarction will continue to have chest pain and sometimes laboratory evidence of continuing or extending infarction. It was thought that emergency aortocoronary byapss in these patients might halt the continuing infarction of myocardium. However, a recent report of several such patients described a 100 percent operative mortality./19/ Further information must be awaited before this treatment can be fairly evaluated.

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ECHOCARDIOGRAPHY

MAJ Richard S White, MC

As the use of more sophisticated invasive techniques grows so does the complication rate as well as the length of the procedure and the discomfort to the patient. As a consequence increasing interest has been generated in various noninvasive techniques of assessing cardiac function and pathology. Echocardiography (ultrasound cardiography) has proven to be a useful noninvasive technique that involves no danger or discomfort to the patient.

The first known use of ultrasound as a cardiac diagnostic tool was described in 1950 by von Keidel./1/ In 1954 Edler and Hertz /2/ used reflected ultrasound to detect mitral valve disease. Since that time many papers have appeared describing the use of this technique in the diagnosis of various forms of heart disease.

The equipment used consists of a small piezoelectric crystal (usually $BaSO_4$) through which electric current is passed, setting up vibrations of the crystal. The frequency of the sound emitted depends on the frequency of the current applied to the crystal./3/ The frequencies used in this technique are all above the range of human audibility (ultra sound). The apparatus applied to the chest houses the crystal and acts as both transmitter and receiver. The transmitter sends one to two thousand short bursts of energy per second. The total duration of those signals is extremely short so that the crystal acts as a transmitter for one millisecond and a receiver for 999 milliseconds of each second./4/

As any sound wave passes through areas of different densities some of it is reflected in many directions. That sound which is reflected back toward the source is received by the transducer, converted to electrical energy, amplified and displayed in several ways. The commonly used displays are termed A and B mode. The A mode is an oscilloscope screen with markers showing the distance of the reflecting interface from the

transducer. The screen has a variable scale marked off in millimeters and centimeters. The distance measurement is based on the fact that sound travels through the human body at an average speed of 1540 millimeters/second./3/ The range is 1476 mm/sec for fat to 1568 mm/sec for muscle. However, bone conduction is more than 3000 mm/sec so one must take care not to place the transducer over bony structures when "looking" at the heart. The B mode is a time scan presentation in which the reflected beam travels from the bottom to the top of the screen displaying a two dimensional presentation of the motion of the reflecting structures. Figure 1.

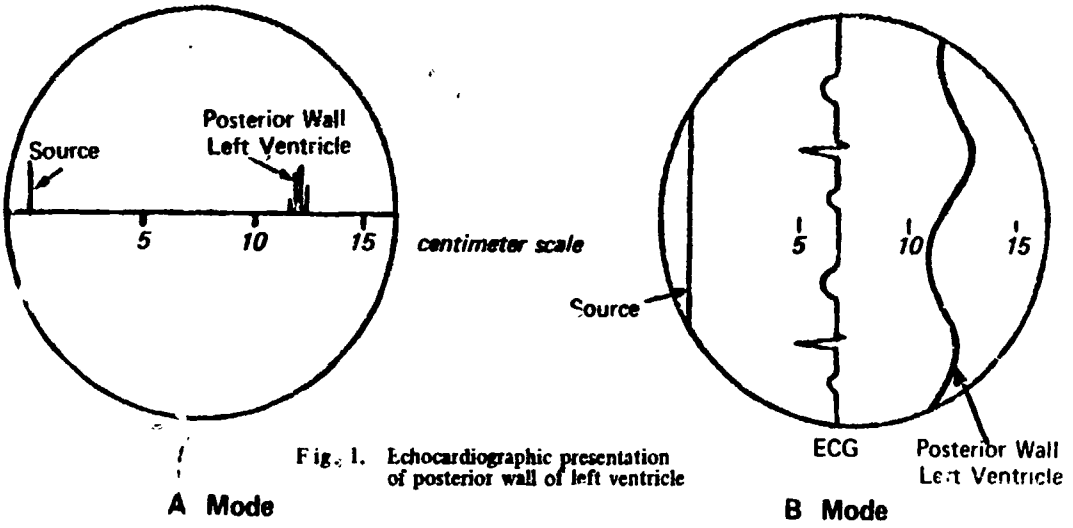

Fig. 1. Echocardiographic presentation of posterior wall of left ventricle

The identification of the echos of the various structures is based on a number of factors, the most significant of which is experience. The distance of the echo from the transducer or chest wall helps identify the source of the echo. However, the characteristics of the motion seen on the screen also help to identify the source. For example, the septum and the posterior wall of the left ventricle have a sine wave type of back and forth motion while the mitral valve has a characteristic flickering motion with a rapid forward motion and a slower return to the posterior position. Finding the echo of that small, rapidly moving anterior leaflet can be a very frustrating experience. Published reports from experienced echocardiographers state that it takes from 10-15 minutes to get an echo of the mitral valve./5,6/ The anterior and posterior walls of the ventricles are the easiest to find followed by the interventricular septum and then the arteriovenous (AV) valves. Proof of the location of the septal and posterior wall echos has been obtained recently by injecting cardio-green dye into

the left ventricle while the echocardiogram is being performed/ The green dye itself echoes, resulting in opacification of the left ventricular chamber area./7/

The technical difficulties that result in time-consuming and inadequate studies are numerous./8/ Even when the experience factor has been mastered there are many more road blocks to using echocardiography successfully. Since the sound waves are virtually completely damped by passage through air, the presence of lung tissue between the transducer and the heart makes it virtually impossible to get a good echo. Having the patient exhale fully while in the right or left lateral decubitus position will correct this problem in all but the markedly emphysematous patient.

Fat also absorbs enough sound to severely limit the usefulness of ultrasound in obese patients. Lower frequency waves go through fat better but higher frequencies give better definition to the reflected sound. Any form of cardiac displacement such as seen in deviation of the diaphragm, obesity, mediastinal shift and vertical heart contributes to unsatisfactory results by causing a longer search for the proper echoes or hiding the structures behind the sternum.

Previous surgical scars in the chest wall or the heart also add to the problems for the echocardiographer.

There are additional hazards of AV valve evaluation — many of the nearby structures (septum, left ventricular wall, papillary muscle, valve annulus and chordae) mimic the motion of the valves./9/ This is especially significant in the presence of AV valve stenosis when the valve motion is less rapid. Sixty cycle electrical interference or muscle noise are of such relative low frequency that they fortunately have no effect on the echocardiogram.

USES OF ECHOCARDIOGRAPHY

The Echo of the Normal Mitral Valve

Echocardiography has found its greatest use in the assessment of mitral stenosis. Some are so adept at this that it is used as a basis for surgical decision without the benefit of catheterization data.* Edler and Hertz /2/, in 1954, first

*Noones D. Personal Communication. Doctor Noones was formerly at the University of Pennsylvania School of Medicine

described the changes that occur in the normal and diseased mitral valves as seen by the echocardiogram. Figure 2 shows the events that occur during the cardiac cycle of a normal mitral valve and the corresponding echo visualization.

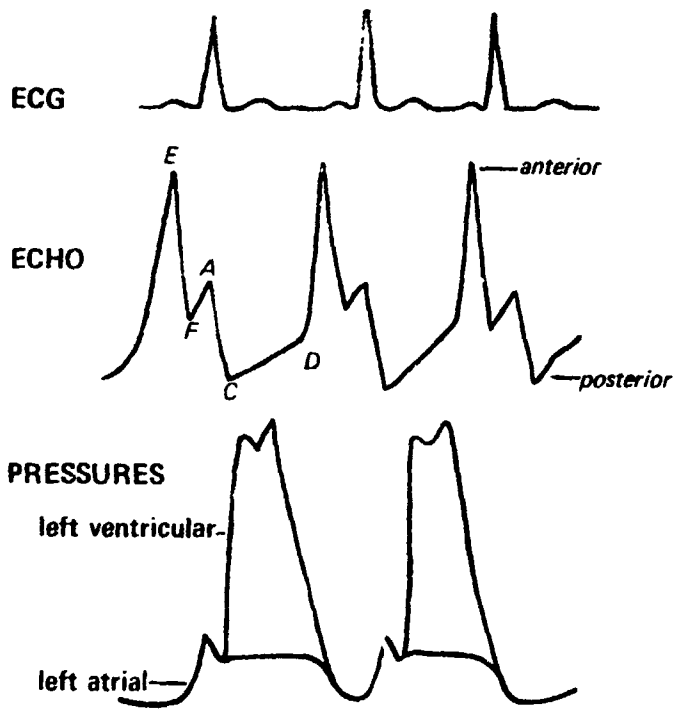

Fig 2 Normal echocardiographic events and their relationship to electrocardiogram (ECG) and intracardiac pressures *LEGEND*: *D* = Mitral valve opens. *E* = Maximal anterior motion of mitral valve. *E-F* = Rapid filling phase of left ventricle. Left ventricle fills passively Valve floats closed to a more posterior position F *A* = A-wave of atrial contraction, presystolic anterior motion *A-C* = Valve closes as ventricle contracts

Figure 2 shows the B mode excursion of the mitral valve rotated 90 degrees clockwise from the presentation seen on the oscilloscope screen. The anterior mitral leaflet is best found on the A mode by recognizing its characteristic flicking motion between the posterior wall of the left ventricle and the intraventricular septum. The transducer is placed at the 4th left intercostal space, one to five centimeters from the left sternal border, and pointed directly posterior until the characteristic back and forth motion of the posterior wall of the left ventricle is seen. Then the transducer is slowly pointed slightly medial and upward until the mitral valve motion is

soon. This maneuver is not always successful so in many patients a search must be made in all directions. On the B mode presentation the AV valves are the only structures in the normal state that have such a pronounced double-peaked motion. The AV valve leaflets have the greatest excursion of any of the cardiac structures (2-3 cm in normal hearts).

MITRAL STENOSIS

Edler and Hertz /2/ discovered that the motion of the mitral valve that was most consistently affected by mitral stenosis (MS) was the posterior motion (E-F, Figure 2) as the valve floats closed during passive left ventricular filling. In mitral stenosis, the ventricle fills slowly (<50 percent of left ventricular filling occurs passively in moderately severe mitral stenosis compared to >60 percent in the normal) /10/ and the valve is held open (anterior leaflet in the anterior position) by the pressure gradient between the left atrium and left ventricle. The characteristic echo of mitral stenosis is seen in Figure 3.

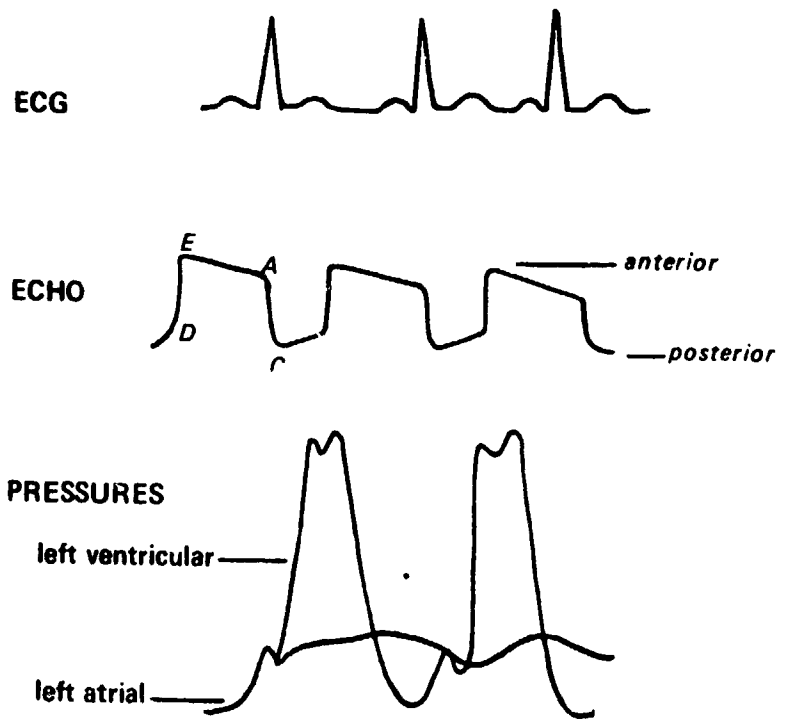

Fig 3 Echocardiogram of mitral stenosis and its relationship to ECG and intracardiac pressures. Legend is given on Figure 2, opposite page.

As the mitral stenosis becomes more severe the A wave decreases and disappears so that the E-F slope gradually blends into the E-A slope. It is this slope or rate of posterior motion of the anterior leaflet of the mitral valve that has been correlated with the degree of mitral stenosis on the basis of catheterization data and surgical measurement of the valve area.

TABLE I shows the most widely accepted values for estimation of mitral valve area (MVA) along with the range of values reported./2,6,8,9-14/ In addition to the slope of the valve motion, the excursion amplitude gives further information about the valve. The normal valve moves 18-30 mm with each cardiac cycle. As the valve becomes more stenotic the motion becomes more restricted. When the excursion is less than 10 mm the values listed on TABLE I lose their reliability. The lower ranges of excursion amplitude are seen with greater degrees of valve and annulus calcification.

TABLE I

VALUES FOR ESTIMATION OF MITRAL VALVE AREA

		SLOPE		AMPLITUDE	
		Average	Range	Average	Range
		mm/sec		*millimeters*	
Normal		125	80-200*	22	18-30
MITRAL STENOSIS	*Valve Area*				
Severe	*1.0 cm^2*	...	10-30	20	10-30
Moderate	*1.0-1.7 cm^2*	...	10-47	...	...
Mild	*1.7-3.0 cm^2*	...	40-80†	...	..
MITRAL INSUFFICIENCY		180	110-360	33	20-45

*All normals reported were over 80 mm/sec

†Insignificant mitral stenosis usually over 40 mm/sec

Combined use of phonocardiography and echocardiography has helped clarify the genesis of the opening snap in mitral stenosis. The sound occurs at or near the E point on most anterior excursion adding weight to the theory that it is the sudden deceleration of the descending mitral ring and valve that causes the opening snap. Mitral insufficiency changes the contour of the echo when seen alone or in association with mitral stenosis. The E-F slope takes on a concave of "ski-jump" appearance

In both mitral insufficiency alone or with mitral stenosis the excursion of the leaflets is increased and the slope (E-F) is increased./5,15,16/ Values above 150 mm/sec are usually seen in isolated mitral insufficiency.

PERICARDIAL EFFUSION

Another of the major uses of echocardiography is the detection of pericardial effusion. The A mode is as useful as the B mode for this entity. In the normal patient the posterior wall of the left ventricle and the posterior pericardium move together. When separated by an effusion the pericardium remains relatively stationary and the myocardial wall has its usual cyclic motion. Most authors /17-21/ consider a separation of at least 1.0 cm necessary to make the diagnosis of effusion. Once the diagnosis has been made by echocardiography the technique can also aid in therapy./22/ Rather than using the chest roentgenogram to determine the presence of suspected residual fluid, an "echo" can be done at the bedside before the procedure is terminated so that further attempts can be made immediately if the "echo" is still positive. Occasionally the effusion will be concentrated in the anterior pericardial space. This situation can also be diagnosed by echocardiography. Effusions as small as 50 cc have been detected in animal experiments. Most authors report that small effusions of 100 cc can be consistently detected in humans. One of the puzzling features of pericardial effusion is electrical alternans. This phenomenon disappears when the fluid is withdrawn. Echocardiography has confirmed the angiographic finding that the heart swings like a pendulum in the fluid filled pericardial space /17/ simultaneously electrocardiography shows the voltage varying with each swing. Figure 4.

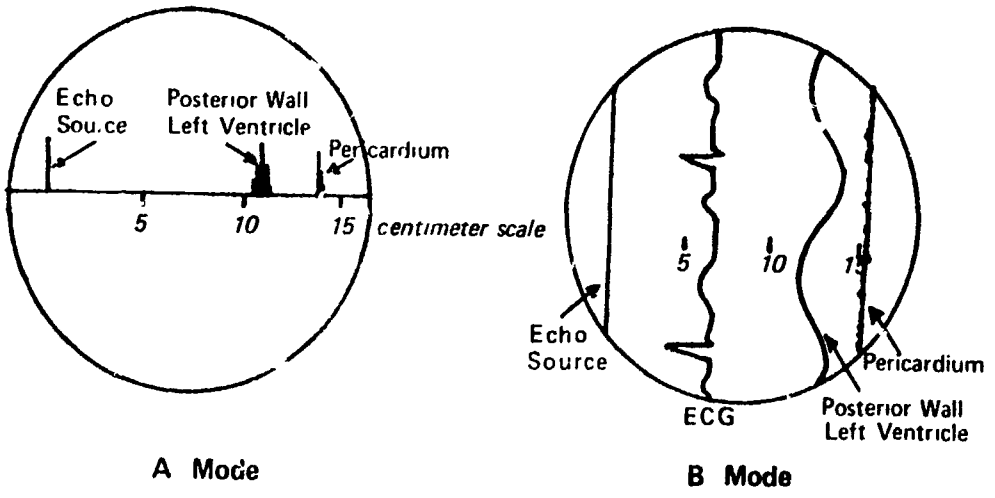

Fig. 4 The separation between ventricular wall and pericardium as seen by echocardiogram in pericardial effusion.

OTHER USES OF ECHOCARDIOGRAPHY

Many other aspects of cardiac health and disease have been evaluated by ultrasound techniques. The accompanying TABLE II lists the suggested positions of the transducer for locating the structures involved. There is great variety and overlap in these suggested positions. In addition, the echocardiographer learns from experience that positions different from those listed will often give a satisfactory recording.

Determing the size of various structures within the heart has been successfully done, and surgical and angiographic results have good correlation. Left and right ventricular size has been determined in a number of conditions./23/ Ratios for normal and abnormal situations have been determined. As one would expect, left to right shunts and right ventricular diastolic overload consistently increase the distance from the anterior heart wall to the right side of the septum. Mitral insufficiency, aortic insufficiency, and gross congestive heart failure cause dilation of the left ventricle. The left ventricular wall thickness has been measured by a complicated technique described by Feigenbaum./24/ Echocardiographic estimation of left atrial size has been shown to be superior

to x-ray and compares very well with angiography./25/ Sizing of the aortic root when replacing the aortic valve with homograft, heterograft or fascia lata valves is an extremely valuable preoperative measurement. One active pediatric cardiology center saves valuable pump time by starting construction of the fascia lata valve before the chest has been opened on the basis of aortic root size determined by the echocardiographer.*

TABLE II

SUGGESTED POSITIONS OF TRANSDUCER FOR LOCATING STRUCTURES

STRUCTURE	POSITION	DIRECTION
Mitral valve	3rd-5th left intercostal space (4th preferred); 1-5 cm (2-4 cm usually) lateral to left sternal border	Slightly posterior, superior
Tricuspid valve	4th-5th left intercostal space; 2-5 cm lateral to left sternal border	Anterior and right of mitral valve
Right and left ventricular cavity	4th left intercostal space	Posterior, slightly lateral and inferior
Left atrium	3rd left intercostal space	Posterior, medial, slightly superior
Posterior left ventricular wall	4th left intercostal space	Posterior
Aortic outflow	4th left intercostal space	Medial and superior to to mitral valve
Idiopathic hypertrophic subaortic stenosis	3rd-4th intercostal space, 1-4 cm lateral to left sternal border	Superior and medial

The search for aneurysms of the abdominal aorta normally leads to angiography. Ultrasound can readily give us the internal diameter of the aorta and an estimation of the wall thickness./26/ Another technique using a transducer transcribing an arch (called B-Scan mode) gives a two-dimensional cross section of the abdominal aorta./26/

Numerous other anatomical and functional abnormalities of the heart can be evaluated by ultrasound. Recently atrial myxoma has been clearly seen on the echogram as a solid echo-producing structure behind the anterior leaflet of the mitral valve./27-31/ Clots of the left atrium will also show as similar sound reflecting defects of the left atrium.

*Kaplan S Personal communication. Doctor Kaplan is Chief, Pediatric Cardiology, University of Cincinnati School of Medicine.

The normal tricuspid valve (TV) has motion that is similar in character (double peaked) and speed to the mitral valve. Joiner et al /32/ gave 60-125 mm/sec as the normal range of TV motion. They also found tricuspid slopes of 8-30 mm/sec in stenotic lesions.

Aortic insufficiency (AI) has been evaluated by the echocardiogram. It has been shown that the regurgitant stream causes a fluttering motion of the anterior leaflet of the mitral valve as the regurgitant stream and the left atrial flow strike the valve./33/ This mechanism has been thought by some to account for the Austin-Flint murmur of aortic insufficiency. However, this fluttering occurs early in diastole, while the Austin-Flint murmur is a mid to late diastolic finding.

The understanding of idiopathic hypertrophic subaortic stenosis (IHSS) has been greatly enhanced with the use of ultrasound./34-36/ With the transducer focused on the septum and the anterior leaflet of the mitral valve while monitoring simultaneous pressure and phonocardiographic traces, it has been shown that there is an anterior motion of the anterior leaflet of the mitral valve toward the septum, sometimes touching the septum as the obstruction and the murmur commence. The thickness of the septum can also be measured with ultrasound.

The most recently described use of echocardiography is to visualize the prolapse of the posterior leaflet of the mitral valve in the various conditions that cause that type of mitral insufficiency./37/ By directing the beam slightly posterior and inferior to the anterior leaflet the excursion of the posterior leaflet can be observed.

Prosthetic valves have been evaluated by the use of ultrasound./38-39/ The most useful measurement is the speed at which the poppet makes its excursion. It is well-known that ball variance and thrombotic material on the valve slow the speed of poppet travel. The diameter of the ball can be measured to determine if there is ball variance.

A potentially valuable use of ultrasound has been reported by Feigenbaum et al /40/ and Popp and Harrison./41/ Based on the assumption that a change in the minor axis of the left ventricle during ventricular contraction gives a reasonably accurate estimation of change in left ventricular volume, stroke volume may be determined. The beauty of this technique is that multiple determinations can be made without harm or discomfort to the patient.

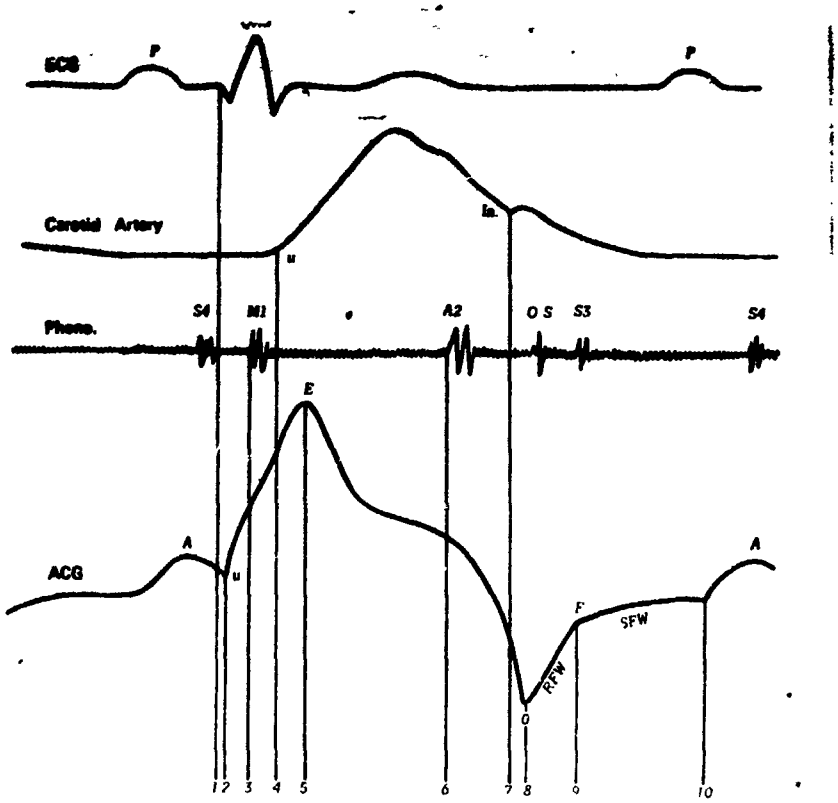

FIG. 1. **Indirect Reference Tracings**
The points indicated in the diagram are used in measurement of cardiac time intervals. The vertical lines *(numbered left to right 1 through 10)* have been drawn so as to denote sequence of events and to aid in the comparative reading of four types of indirect reference tracings.

ECG = electrocardiogram with *P-wave* and *QRS-wave complex* indicated

Carotid Artery = indirect carotid artery pulse tracing
u = upstroke [point of origin of the carotid artery upstroke (CA$_u$)]
In. = carotid incisura [point separating systolic and diastolic phases of carotid pulse (CA$_{In}$)]

Phono. = phonocardiogram
S4 = fourth heart sound
M1 = initial high frequency vibrations of mitral component of first heart sound
A2 = initial high frequency vibrations of aortic component of second heart sound
O.S. = opening snap
S3 = third heart sound

ACG = apexcardiogram
A = left atrial contraction
u = upstroke of ACG
E = ejection point
O = nadir
RFW = rapid filling wave
SFW = slow filling wave

from LGH, 1971

CONGENITAL HEART DISEASE

In the evaluation of congenital heart disease ultrasound has aided in the diagnosis and management of several conditions. The slope of mitral valve motion is altered by increased flow across the mitral valve as noted above in the discussion of mitral insufficiency. Therefore, those conditions with a left to right shunt at the ventricular level and subsequent increased flow across the mitral valve cause increased E-F slope./42/ Figure 2. Tetralogy of Fallot without reversal of flow across the ventricular septal defect causes the same changes; and with successful repairs of the ventricular septal defect, the changes return to normal. Patent ductus arterosus also causes an increase in the E-F slope of the mitral valve while atrial septal defect only causes an increased flow across the tricuspid valve and thus increases its slope. Ostium primum atrial septal defect with increase in flow across both AV valves causes the expected echocardiographic changes. Additional evidence of shunting can be obtained by measuring the relative size of the ventricular chambers. All conditions with left to right shunting at the atrial or ventricular level increase the anteroposterior diameter of the right ventricle which can be appreciated using either the A or B mode. In infants with suspected hypoplastic right or left heart the presence or absence or relative size of each chamber can be measured if the septum can be found./43/ If no septum can be seen, then one has good evidence that he is indeed dealing with a single ventricle.

The seldom-found condition if discrete subaortic stenosis has been "seen" on echocardiography as a structure that moves like the mitral valve but has an excursion of less than 15 mm and appears as a thinner shadow compared to the mitrel valve./39/ As mentioned above, ultrasound has been used to size the aortic root prior to valve replacement.

COMMENT

Ultrasound is an innocuous procedure that has proved totally safe and painless for the patient. This technique has been shown in the few short years that it has been available to have a wide variety of clinical applications. We have only begun to realize the potential uses of this technique. Its main drawbacks at the present time are the lack of standardization of normals and abnormals plus the time required for even the experienced echocardiographer to obtain satisfactory and clinically useful results. Since ultrasound is well-established as a clinically useful tool in pericardial effusion and mitral valve disease, it is only a matter of time until many of the invasive methods used today will be complemented or replaced by this technique.

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SERUM DIGITALIS LEVELS
New Techniques of Measurement

MAJ Carroll M. Martin, Jr., MC

Although much knowledge and understanding about the biochemistry and metabolism of cardiac glycosides has been accumulated since Withering's original accounts of the drug in 1785, only recently have clinically reliable methods of assaying blood levels of these drugs become available. Rapid and reliable determinations of serum digitalis glycoside levels will aid the clinician faced with the dilemma of whether to withhold or administer these drugs in cases of possible digitalis toxicity. The problem of determining blood levels is made difficult because, in the usual therapeutic setting, exceedingly small amounts of digitalis circulate in the blood. Another problem is the interpretation of blood levels which is made more difficult by the fact that digitalis has a low toxic to therapeutic ratio./1,2/ This discussion reviews the current status and clinical application of available quantitative assays of blood levels of cardiac glycosides.

It has been shown that during maintenance therapy with digoxin the myocardial concentration bears a relatively constant ratio to the serum concentration (29:1), as measured by radioactive digoxin./3/ Hence, the accurate determination of serum values seems to be a rational approach to evaluate the myocardial concentrations of these drugs. Straight forward biochemical assays have proven to be laborious, time-consuming and insensitive and have thus not received widespread clinical application. A measurement of the inotropic effect of cardiac glycosides using indirect assessment of left ventricular ejection time was pioneered by Weissler et al /4/ and is a valuable technique. However, it obviously gives no information regarding the quantitative amount of circulating drug related to its physiologic effects.

Friedman and Bine /5/ have developed the most sensitive nonradioactive assay for digitalis glycosides. This assay utilizes a duck embryo bioassay technique and is able to detect levels of 25 nanograms/milliliter of digitoxin. However,

this is inadequate for evaluating normal blood levels. The technique requires laborious urine collections; results are difficult to interpret because digitalis glycosides are also excreted fecally, and active metabolites as well as the originally administered drug appear in the urine.

During the 1950s, isotopically labeled digitalis derivatives were prepared./3,6/ This allowed development of methods for accurate quantitation of nanogram amounts of ^{14}C or tritium-labeled digoxin and digitoxin. This advance enabled investigators to define the pharmacodynamics of the digitalis glycosides. It also yielded major advances and understanding of absorption and protein binding /7/, tissue distribution /3,8/, and routes of excretion of digoxin and digitoxin./3,9/ Another important observation was that serum digoxin concentrations of patients on usual maintenance doses were in the one to two ng/ml range /10/ and the serum concentrations were approximately ten-fold higher with digitoxin./11/ In 1967, Lukas and Peterson /12,13/ reported a double isotope derivative method which was specific and precise, but required several days to do a small number of examinations. This method uses tritated digitoxin to monitor procedural losses of digitoxin during extraction and conversion to a ^{14}C-triacetate derivative which can be isolated, purified, and quantitated. This method has not been applied to determinations of serum digoxin levels. Also, in the 1950s it was shown that extremely small concentrations of cardiac glycosides inhibit the uptake of radioactive potassium by human red cells./14/ It was further demonstrated that both efflux and influx of sodium and potassium were inhibited by as little as 1.0 ng/ml of digoxin /15/; and, of a large group of steroids, that only the digitalis glycosides inhibit potassium uptake in physiologic concentrations./15,16/ The inhibitory activity of these drugs, it is speculated, is attained by inhibition of the Na-K activated membrane adenosine triphosphatase (ATP-ase)./17/

Utilizing these facts, Lowenstein /18/, in 1965, devised an assay for digoxin based on the inhibition of the red cell uptake of ^{86}Rubidium (^{86}Rb). This isotope was chosen because of its shorter half-life (19 days) compared to potassium isotopes. This assay is precise and demonstrates a sensitivity as small as 1.0 ng/ml. In his original assay there was a seven percent incidence of patients not taking digitalis having a positive level greater than 1.0 ng/ml, i.e. some other plasma constituent which inhibited red cell ^{86}Rb uptake. Also, this method did not allow for determinations of digoxin in other body fluids such as urine because of hemolysis of the red cells.

In a subsequent modification, Lowenstein and Corrill /19/ developed an extraction procedure with methylene dichloride which eliminated the false positives, allowed assay in other fluids, and increased the sensitivity of the assay for both digoxin and digitoxin.

Some workers have not been able to reproduce this method /20,21/; however, most others have been able to use the assay /22-28/ and made further modifications to increase its sensitivity. In a critical analysis of methodology and careful attention to laboratory technique, Bertler and Redfors /28/ have modified this technique to an even lower limit of sensitivity (between 0.3 and 0.5 ng/ml of digoxin). The specificity of this ^{86}Rb assay seems quite good and it has been shown that other drugs such as spironolactone, chlorthiazide, ethacrinic acid, furocimide, guanethadine, bethanadine, prednisone, quinine, and bishydroxycoumarin do not interfere with the method./23,28/

Radioimmunoassay of polypeptide hormones is an established technique. These methods rely on competition between an unlabeled molecule present in the fluid to be assayed and a radioactively labeled form of the substance, added in vitro, for a limited number of antibody binding sites. This approach was first applied to the measurement of digitalis glycosides in 1968 by Oliver et al./29/ The development of antidigoxin antibodies of high affinity and specificity soon allowed for the development of a radioimmunoassay of sufficient sensitivity to be clinically useful./30-33/ Although the cardiac glycosides are not antigenic in their clinical form, they can be coupled as haptens to convenient carriers such as albumin. When injected into rabbits, antibodies of high affinity and specificity for the glycoside can be obtained. Smith et al /33/ have modified their radioimmunoassay by separating bound from free labeled digoxin by a dextran coated charcoal technique, which yielded such a remarkable sensitivity that extraction of the glycosides with organic solvents, a step common to all other techniques, was obviated. This greatly enhanced the rapidity and simplicity of their assay technique.

Other approaches to the quantification of blood levels of digitalis glycosides include a sodium-potassium ATP-ase inhibition assay for digitoxin /34,35/, and a serum digoxin assay based on enzymatic isotopic displacement of tritiated digoxin from brain sodium-potassium ATP-ase./36,37/ The ATP-ase inhibition assay is not applicable to digoxin because of apparent difference in enzyme binding./35/ A gas chromatographic assay has

also recently been described./38/ In this technique, digoxin is extracted from the serum with methylene chloride, separated by thin layer chromotography from interferring substances and reacted with heptafluorobutyric anhydride to form the digoxigenin-heptofluorobutyrate. This is purified by an additional extraction of benzene: ethylacetate and injected into a gas chromatograph. The overall recovery is 30-40 percent and the minimal detectable amount is 40 picagrams. Although this technique is currently limited to digoxin, it is in the process of being adapted to digitoxin and to digoxin metabolites. The time for a single determination is two hours in an emergency and 4-5 hours with routine determinations. These last three assay methods are new and relatively not fully assessed.

Comparison of these various methods must be considered in terms of specificity, sensitivity, precision, rapidity and ease of performance. Data on these various points have been extracted from the literature and are summarized in TABLES I and II.

Digoxin assays require more stringent sensitivity and resolution than digitoxin assays since blood levels are lower by a factor of 10. The difference in plasma levels between these drugs may be due to a greater binding of digitoxin by serum albumin./7/ Various specificity data for ^{86}Rb digoxin assays have been reported but recent modifications /28/ have eliminated most of the false positive results. The specificity of radioimmunoassay is largely a function of the antiserum employed. Therefore it is important to characterize the antibody population to be used in terms of hapten, binding affinity, and specificity. No false positives have been reported in recent radioimmunoassay procedures.

Disparity in serum or plasma digoxin concentrations have been reported by different investigators using various techniques. The reported values for the mean concentrations are functions of the maintenance dose administered, and the time after dosage that the level is determined. Values reported from ^{86}Rb methods are both higher and lower than those for radioimmunoassay. TABLES I and II. In a recent report /40/, blood values of digoxin in children determined by radioimmunoassay were given.

Digitoxin assays give large serum values as previously mentioned. TABLES I and II A sensitivity of 10 ng/ml has been reported for all assay techniques. Precision seems to

vary more from technique to technique than with digoxin assays. Elimination of false-positive results has been reported for radioimmunoassay, ^{86}Rb uptake inhibition /19/, double isotope derivative methods /13/, and ATP-ase inhibition method /34,35/. Somewhat higher levels are measured by ATP-ase inhibition method /35/ as compared to radioimmunoassay /39,41/. This may reflect a greater ability of metabolites of digitoxin to inhibit brain sodium-potassium, ATP-ase, and to displace tritiated digoxin from antibody binding sites./41/

The newly described technique of gas chromatography assay for digoxin is reported to be easily adapted to determination of digitoxin. Although all these methods have valuable clinical usage, it has been speculated that new developments in mass spectometry during the next few years will render all of them obsolete./42/

Clinical interpretation of these quantitative techniques rests upon the assumption that a stable equilibrium exists between blood and tissue levels which is probably true within 4-6 hours after an oral dose and sooner following an intravenous dose /41/ and that the blood level reflects total body and myocardial concentration. This has been shown to be true in patients receiving digoxin./3,43/ Although alterations in binding of digoxin to myocardium with changes in thyroid function /44/ and potassium and sodium levels /45,46/ have been shown in animal experiments, it seems unlikely that such variations would negate the value of these determinations in clinical situations.

The data regarding the constancy of blood to myocardial digitoxin concentration ratios are inadequate to allow definite conclusions./41/ Marcus /47/ has indicated caution in the interpretation of serum digitoxin concentrations, because this glucoside, unlike digoxin, is largely metabolized to other forms of varying cardiac activity prior to extraction.

Only recently is the clinical application of these techniques being studied. Perhaps the most intriguing of the techniques to the clinician is the one by which he tries to identify patients who have toxic glycoside concentrations./47/ There is general agreement that patients with clinical and electrocardiographic signs of digitalis toxicity have higher blood levels than nontoxic patients. Smith and Haber /39/ found a mean plasma concentration of digoxin of 3.3 ng with the radioimmunoassay technique in toxic patients; however,

TABLE I

DIGOXIN ASSAY METHODS*

METHOD	SENSITIVITY	PRECISION	SPECIFICITY	RAPIDITY	NORMAL VALUES & REFERENCES
^{86}Rb uptake inhibition	< 1.0 ng/ml	SD ± 5%	No false positives after extraction	4 hours	0-5.0 ng/ml [2,3,18-19,25] 0.4-1.0 ng/ml [28]
^{86}Rb uptake inhibition	< 1.0 ng/ml	SD ± 5%	No false positives. No interference secondary to diuretics or antihypertensive medication	3-4 hours	0.9-1.5 ng/ml [28] 0.8-4.5 ng/ml [2,23,26]
Radioimmunoassay	0.2 ng/ml	SD ± 4%	No false positives	1 hour	0.8-2.4 ng/ml [31] 0.7-2.1 ng/ml [40]
Gas chromotography	0.4 ng/ml	SD not stated	No false positives	4-5 hours	1.0-3.0 ng/ml [38]

*Adapted from Smith TW, Haber E: *Amer J Med Sci* 259:301, 1970

they found considerable overlapping. Smith and Haber/48/ also reported that in a total of 131 patients, 90 percent of the patients who had no clinical nor electrocardiographic evidence of toxicity had blood digoxin levels less than 2.0 ng/ml, while in 87 percent of those with evidence of toxicity the level was greater than 2.0 ng/ml. Kalman and Watson /38/, using gas chromatography on a limited number of clinically toxic patients, have reported that digitalis toxicity levels are probable about 4.0 ng/ml. Ritzman et al /25/, using ^{86}Rb assay, reported digoxin levels greater than 5 ng in 7 of 11 toxic patients and digitoxin levels of 39-51 ng in one toxic patient. Bently et al /35/, using ATP-ase inhibition assay techniques, suggested that digitoxin levels greater than 45 ng required consideration of digitalis toxicity. However, it must be emphasized that no clear cut blood level differentiates maintenance from toxic levels. Perhaps the most important factor in determining the sensitivity of digitalis is the nature of the underlying cardiac disease./49/ Recent experience /50/ suggests that young patients with normal hearts tend to respond by developing life-threatening ventricular arrhythmias.

A recently reported study /40/ of digoxin levels in eleven infants determined by radioimmunoassay showed that or a maintenance dose of 0.007-0.01 mg/lb the blood level 5 hours after dosage was 2.3 ± 0.9 ng/ml. This was significantly greater than the mean level

TABLE II

DIGITOXIN ASSAY METHODS*

METHOD	SENSITIVITY	PRECISION	SPECIFICITY	RAPIDITY	NORMAL VALUES & REFERENCES
^{86}Rb uptake inhibition	1.0 ng/ml	SD ± 5%	No false positives after extraction	4 hours	10-50 ng/ml [19]
^{86}Rb uptake inhibition	1.0 ng/ml or less	SD +0.9 ng/ml	No false positives	5 hours	1.0-37 ng/ml [25]
Radioimmunoassay	< 2.0 ng/ml	SD ± 5% SE ∓ 1.6 over range of 5-50 ng/ml	No false positives	1-2 hours	4.0-30 ng/ml [39] 4.0 60 ng/ml [29,39]
Radioimmunoassay	1.0-2.0 ng/ml	Concentration dependent; coefficient of variation 11.0-31.7%	Occasional false positives	One day	5.0-40 ng/ml [27]
Double isotope dilution derivative	10 ng in 3-10 ml of plasma	Concentration dependent; coefficient of variation 4.0-20%	Excellent	Four days	10-56 ng/ml [13]
Na-K ATP-ase inhibition	< 10 ng/ml	SD 2.9-5.2% over range 10-100 ng	Occasional false positives	4 hours	10-40 ng/ml [35]
Gas chromatography†	...	...	...	...	...

*Adapted from Smith TW, Haber E: *Amer J Med Sci* 259:301, 1970
†Not applied to digitoxin [38]

in adults (1.4 ± 0.7 ng/ml); this maintenance dose was 0.31 ± 0.19 (SD)mg. There was no evidence of toxicity in these infants even though 7 of the 11 had levels greater than 2.0 ng/ml. It was concluded, therefore, that infants tolerate significantly higher serum concentrations than adults while on usual maintenance therapy.

Another area of potential use of precise blood digitalis glycoside levels is in further delineating the clinical pharmacology of the drugs, /39,51-54/ for example, in the study of GI absorption of the drug in malabsorption states. A new area of investigation is evaluation of the half-life, onset and duration of the inotropic effect of cardiac responses combining indirect assessment of contractility and serum glycoside levels./55,56/

In summary, the last 10 years have brought remarkable progress in the ability to accurately and precisely quantify blood levels of cardiac glycosides. Clinical application of these techniques is just beginning to gain widespread appreciation and the future should provide the clinician with a new awareness and skill in managing patients requiring treatment with digitalis and its derivatives.

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Let the medicine therefore be given in doses, and at intervals mentioned — let it be continued until it either acts on the kidneys, or the stomach, the pulse or the bowels; let it be stopped upon the first appearance of any of these effects.

— WILLIAM WITHERING
On Digitalis, 1785

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